Journal of Neonatal Surgery
ISSN (Online): 2226 -0439
Vol. 14, Issue 7 (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Exploring the Anticoagulant Mechanisms in Complementary and Alternative Medicines and Pharmacokinetics and Pharmacodynamics of Novel Oral Anticoagulants

Babita Sahu[1*], Akshi[2], Yuri Verma[3], Debarsi Das[4], Avidipta Hazra[5*]

[1*]Assistant Professor, Hi-Tech College of Pharmacy, Bhubaneshwar, Odisha, India.
Email ID: nayakbabita68@gmail.com
[2] Assistant Professor, Chandigarh University, Mohali, Punjab, India.
Email ID: akshi.e16923@cumail.in
[3] Assistant Professor, Noida International University, Noida, Uttar Pradesh, India.
Email ID: yuri.verma@niu.in
[4] HOD & Professor, Department of Organon of Medicine, Metropolitan Homoeopathic Medical College and Hospital, Sodepur, Kolkata, West Bengal, India.
Email ID: drdebarsi@gmail.com
[5*] Under-graduate, Metropolitan Homoeopathic Medical College and Hospital, Sodepur, Kolkata, West Bengal, India.
Email ID: avidipta.kurchi@gmail.com

***Corresponding Author:**
Babita Sahu,
Assistant Professor, Hi-Tech College of Pharmacy, Bhubaneshwar, Odisha, India.
Email-ID: nayakbabita68@gmail.com

Cite this paper as: Babita Sahu, Akshi, Yuri Verma, Debarsi Das, Avidipta Hazra, (2025) Exploring the Pharmacokinetics and Pharmacodynamics of Novel Oral Anticoagulants. *Journal of Neonatal Surgery*, 14 (7), 422-435.

ABSTRACT

The novel oral anticoagulant medications known as NOACs represent a revolutionary agent group that delivers superior benefits versus traditional vitamin K antagonists for both treatment and prevention of thrombus-related conditions such as atrial fibrillation, deep vein thrombosis, and pulmonary embolism. This paper provides detailed information on NOAC applications across these indications, presenting dosing approaches and treatment strategies tailored to diverse patient populations. Additionally, complementary and alternative medicines (CAMs), including authenticated phytochemical extracts from Traditional Chinese Medicine and India's ancient practices, have demonstrated significant antithrombotic and antiplatelet effects in vitro and in preclinical models. We examine pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of NOACs—dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban-alongside emerging evidence on phytochemical constituents of CAMs like β-sitosterol, flavonoids, detailing mechanisms of action, dose-response relationships, and factors affecting interindividual variability. The present discussion further addresses bleeding risks, limited reversal agent availability, and diagnostic uncertainties in specific patient cohorts. A comprehensive analysis explores advances in specific antidotes, next-generation anticoagulants targeting Factor XI/XII, and personalized medicine strategies. This review utilizes both pharmacological concepts and clinical experience to direct appropriate and safe NOAC utilization throughout different patient groups with an emphasis on potential research paths in evolving anticoagulation treatment approaches and juxtaposition of NOACs and CAMs underscores the need for rigorous dose-finding, authentication protocols, and safety profiling to integrate phytopharmaceuticals into evidence-based anticoagulation therapy.

KEYWORDS: *NOACs, pharmacokinetics, bleeding risk, personalized anticoagulation, anticoagulants, complementary and alternative medicine*

1. INTRODUCTION

Thromboembolic conditions, made up of venous thromboembolism (VTE) and atrial fibrillation (AF)-related stroke position as significant causes of deaths throughout the globe. The World Health Organisation reports that cardiovascular diseases result in 17.9 million annual deaths, which represent 32% of global fatalities through thromboembolic events.[1] India shares global cardiovascular disease patterns because its population faces additional challenges from social and population changes. Research indicates that atrial fibrillation affects more than 4 million Indians, while VTE prevalence

continues to increase at a steady rate, and hospital-based studies show high-risk patients have a 17% prevalence.[2] The rising rates of obesity and diabetes, and an ageing population, alongside lifestyle changes, have made effective anticoagulation strategies more necessary than ever to combat the strong risk factors of thrombosis. The primary oral anticoagulation therapy has relied historically on Vitamin K antagonists (VKAs), with warfarin as the main example. The clinical effectiveness of VKAs exists, but multiple substantial barriers have persisted in their therapeutic deployment since their introduction.[3,4] These anticoagulant drugs have limited therapeutic margins and show wide differences between patients, while needing regular INR testing to achieve effective treatment while reducing bleeding or thrombotic risks. Long-term management of VKAs becomes complicated because these medications show extensive interactions with many foods and commonly used medications. The limited success of monitoring anticoagulation with VKAs in real-world healthcare leads to multiple patient complications and diminished quality of life with escalating healthcare expenses.[5] Novel Oral Anticoagulants (NOACs) received their designation within the last two decades under the alias Direct Oral Anticoagulants (DOACs). The direct thrombin inhibitor dabigatran and direct Factor Xa inhibitors rivaroxaban and apixaban, and edoxaban, and betrixaban have brought a rapid transformation to anticoagulation therapy.[6] The goal of NOACs is to deliver more forecastable PK and PD by offering standardized dosing and immediate effects alongside minimal need for follow-up and few important drug-food interactions. Post-marketing surveillance, along with practical experience, has discovered that NOACs carry certain intricacies, although they provide considerable benefits. Patient-specific factors, which include age extremes and renal or hepatic dysfunction, along with body weight variations and genetic polymorphisms, and concurrent medication use, modify the PK/PD profiles of NOACs.[7,8] The wide range of variability affects both the drug's therapeutic performance and bleeding hazards and safety profile. The lack of routine coagulation monitoring for NOACs exists, but healthcare providers need detailed PK/PD knowledge when treating patients during emergency surgeries or bleeding complications or renal failure, or overdose situations.[9] The four core drug processes, including absorption and distribution and metabolism, and excretion, are regulated by pharmacokinetics in a way that determines the amount of drug reaching systemic circulation. The biological effect of NOACs emerges from the drug concentration at their site of action, according to pharmacodynamic principles, which inhibit thrombin or Factor Xa to stop clot formation. The connection between PK and PD plays a vital role in predicting treatment response variability, and it helps optimise drug schedules and control adverse effects, and develop countermeasures.[10,11] The clinical success of NOACs demonstrated in RE-LY,[12] ROCKET AF,[13] ARISTOTLE,[14] and ENGAGE AF-TIMI-48 trials,[15] does not eliminate important knowledge gaps in their understanding. Scientists continue to research the effects of organ dysfunction on drug exposure as well as pharmacogenetic variability and optimal management strategies for complex clinical situations.[16] The uncertainty extends particularly to elderly patients, along with those who have severe renal impairment and patients with multiple comorbidities, because there is no universally accepted therapeutic range, and standardized monitoring assays do not exist for NOACs. Modern studies on pharmacogenomics, together with PK/PD modelling, will help develop advanced anticoagulation practices toward precision-based medical care strategies.[17,18] Patient-specific anticoagulation management that uses PK/PD profiles of each individual enables better treatment outcomes and reduced adverse reactions. Medical professionals require a deep understanding of NOAC pharmacology to effectively manage bleeding emergencies and surgical procedures because of recent developments in specific reversal agents that include idarucizumab for dabigatran and andexanet alfa for Factor X_a inhibitors. Concurrently, a vast portion of the global population, especially in developing countries, relies on CAMs: recent studies report that approximately 85% of traditional herbal remedies serve 65% of people worldwide and 80% in developing regions.[19] In-vitro and preclinical research has uncovered those bioactive phytochemicals like flavonoids, β-sitosterol) from authenticated herbal sources exert anticoagulant, antiplatelet, and fibrinolytic activities by modulating plasma clotting times, inhibiting thrombin and Factor Xa, elevating intraplatelet cyclic nucleotides, and promoting clot dissolution.[20,21,22,23] Furthermore, the WHO Traditional Medicine Strategy 2014-23 advocates for the integration of CAMs into national health systems, emphasizing the need for robust regulatory frameworks to guarantee the safety, quality, and efficacy of natural products.[24] Programs such as the International Regulatory Cooperation for Herbal Medicines (IRCH) and India's AYUSH department illustrate concrete measures to harmonize standards, promote practitioner training, and foster research collaborations to advance phytopharmaceutical development. Integrating CAMs with NOAC modalities presents unique opportunities and challenges in dose optimization, safety assessment, and standardization. This review provides a unified perspective by dissecting the mechanistic and clinical pharmacology of NOACs-examining molecular targets, PK pathways, PD biomarkers, sources of interindividual variability, and their clinical implications,[25] while concurrently surveying antithrombotic CAMs, from standardized herbal extracts to advanced bioassay-guided fractionation and novel delivery systems. Special emphasis is placed on integrating recent advancements-such as high-throughput phytochemical screening, nano formulations to enhance bioavailability, and early-phase clinical validations of standardized

phytoconstituents-into evidence-based anticoagulation strategies. Moreover, innovations in computational biology, microarray assays, and plant-derived exosome-like nanoparticles have further accelerated the rapid identification and delivery of potent antithrombotic phytochemicals in preclinical models. We address practical challenges including bleeding risk management, limited reversal agents, and diagnostic uncertainties in complex patient cohorts, and explore future directions in pharmacogenomics, advanced PK/PD modeling, and biomarker discovery. By bridging synthetic and phytopharmaceutical approaches, this work aims to inform precision anticoagulation, optimize therapeutic regimens for high-risk populations, and advance clinical practice within contemporary healthcare frameworks.

2. OVERVIEW OF NOVEL ORAL ANTICOAGULANTS (NOACs)

A highly complex system of coagulation cascade controls the equilibrium between haemostasis and thrombosis. The coagulation pathway consists of three sections known as the intrinsic, extrinsic, and common pathways, which end in the formation of thrombin through which fibrinogen transforms into fibrin to stabilise the clot.[26] The activation of Factor X to Factor Xa serves as a key step in the cascade because it enables the protease to convert prothrombin (Factor II) into thrombin (Factor IIa) while using Factor Va as its cofactor. Factor Xa then drives clot stabilisation and platelet aggregation and boosts its production by activating Factors V, VIII, and XI. The pharmacological targets of warfarin and NOACs, together with their associated pathways, are illustrated in Figure 1.

The historical anticoagulation approach used warfarin as a representative of Vitamin K antagonists to block clotting factor synthesis.[27] The approach had major limitations because it produced wide differences between patients and required a small therapeutic range, while requiring regular monitoring. The pharmaceutical industry developed Novel Oral Anticoagulants (NOACs) to provide better control over anticoagulation effects.[28] The two main molecular target groups of Novel Oral Anticoagulants (NOACs) include direct thrombin inhibitors, with dabigatran as the example, and direct Factor Xa inhibitors, which include rivaroxaban and apixaban and edoxaban, and betrixaban. The anticoagulant effect of dabigatran etexilate results from its direct binding to thrombin, which stops both free and fibrin-bound forms of thrombin and prevents fibrin formation and platelet activation.[29] The Factor Xa inhibition mechanism of rivaroxaban and apixaban and edoxaban, and betrixaban prevents Factor Xa activation to stop thrombin generation and clot formation.[30]

NOACs demonstrate better pharmacological properties than traditional Vitamin K antagonists because they have predictable drug actions and require no routine blood tests and show fewer drug-food interactions and start and stop more quickly, and provide better protection against bleeding in the brain. NOACs have achieved widespread clinical success because of their benefits, which provide safer and more convenient anticoagulation therapy to patients who need long-term treatment.

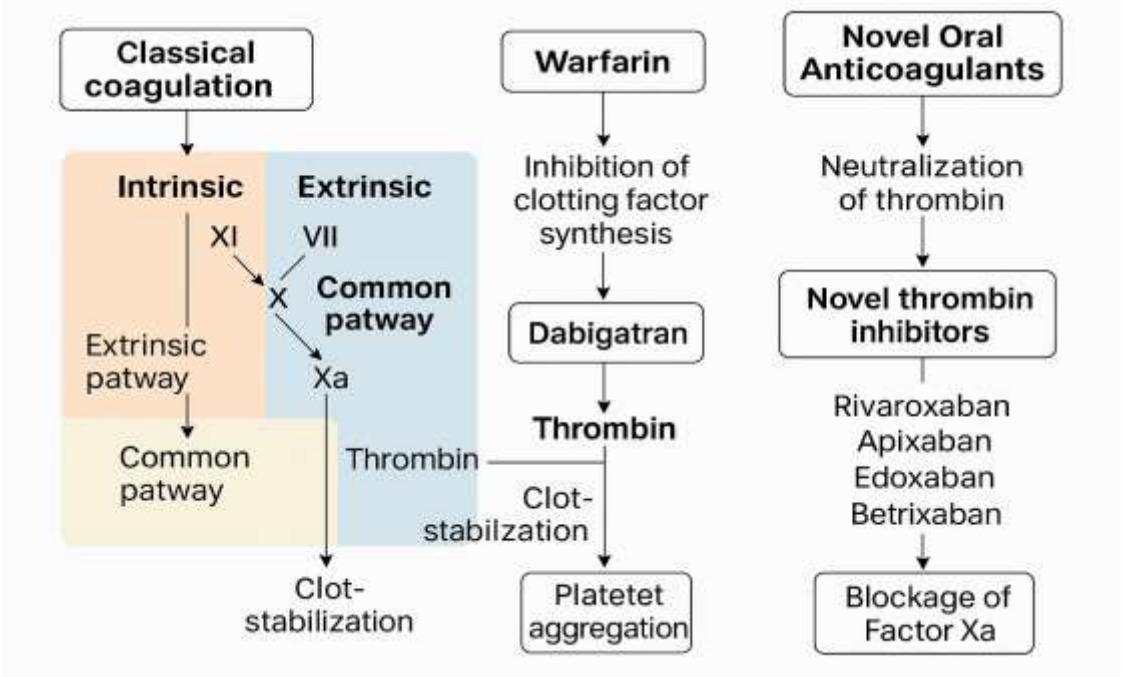


Figure 1: Schematic Representation of the Coagulation Cascade and Sites of Action for Warfarin and Novel Oral Anticoagulants (NOACs)

3. COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAMs) AS ANTICOAGULANTS

A recent study found that around 85% of conventional complementary and alternative medicines fulfil the medicinal needs of roughly 65% of people worldwide and 80% of those living in developing countries.[19] In vitro and preclinical studies have revealed that a range of natural product constituents-such as extracts from traditional herbs and medicinal plants-alongside established traditional medical systems (for example, Traditional Chinese Medicine and India's ancient medical practices) and certain functional foods, possess notable antithrombotic effects.[20-23]

4. ANTICOAGULATIVE MECHANISMS OF COMPLEMENTARY AND ALTERNATIVE MEDICINES (CAMs) FOR POSSIBLE PROPHYLACTIC AND THERAPEUTIC APPLICATIONS

Various plant extracts have been evaluated through various In-vitro or In-vivo studies for their anticoagulant activity (inhibition of plasma clotting activity), inhibition of activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), antiplatelet activity, and clot-busting (clot-dissolving) properties.[31,32,33,34] The integration of advanced multidimensional chromatographic techniques holds significant potential for further fractionating or diluting crude plant extracts, enabling the isolation and identification of bioactive compounds with antithrombotic potential, see on Table 1.

These techniques can help pinpoint specific molecules responsible for anticoagulant or antiplatelet effects, allowing for a clearer understanding of their mechanisms of action and therapeutic value. However, a major challenge in advancing these findings to clinical application lies in the absence of comprehensive dose–response studies. For many plant-derived extracts and isolated compounds, the effective dose ranges—particularly those demonstrating a balance between efficacy and safety—remain undetermined. Without this critical information, it is difficult to proceed with preclinical animal models or clinical human trials. This gap in foundational pharmacological data significantly hampers the development and approval of antithrombotic phytopharmaceuticals, limiting their integration into evidence-based medical practice. To overcome this barrier, systematic pharmacokinetic and pharmacodynamic studies are urgently required.

4.1 Anticoagulant activity via inhibition of coagulation factors

Numerous plant-derived flavonoids and other bioactive compounds directly inhibit key proteases in the coagulation cascade (most notably thrombin and factor Xa) by prolonging APTT, PT, and TT. Flavonoids such as myricetin,[35] quercetin,[36] kaempferol, baicalein, apigenin, acacetin and biflavones like hinokiflavone competitively bind thrombin's active site or exosites,[35] while non-flavonoid prototypes (e.g. plant-derived β-sitosterol) similarly impede thrombin's catalytic function.[31] A few purified serine proteases (e.g., lunathrombase) even exhibit dual inhibition of thrombin and Factor X active (FXa). These mechanisms have been demonstrated in vitro, although comparative potency versus clinical anticoagulants and in vivo efficacy remain to be established. Some of the herbal compounds tested under in vitro conditions demonstrated low anticoagulant potency compared to the commercial synthetic direct inhibitors of thrombin (i.e., dabigatran and bivalirudin); however, the preclinical studies suggest that these compounds are safe to administer.[37,38]

In some instances, the purified active compounds demonstrated less anticoagulant potency than the crude or partially purified plant extract, which suggests that the active components act synergistically to enhance their antithrombotic activity.[32]

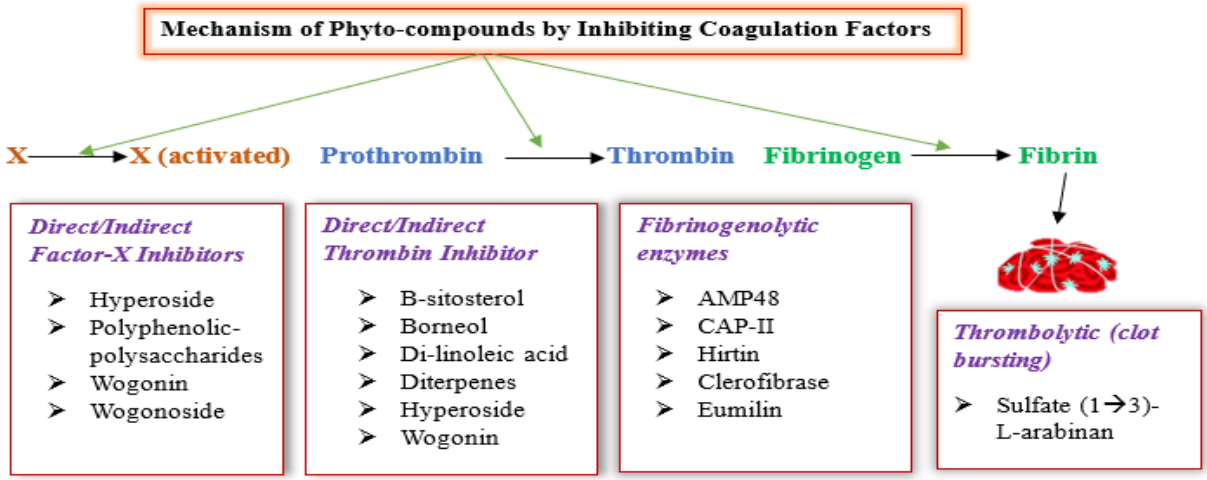


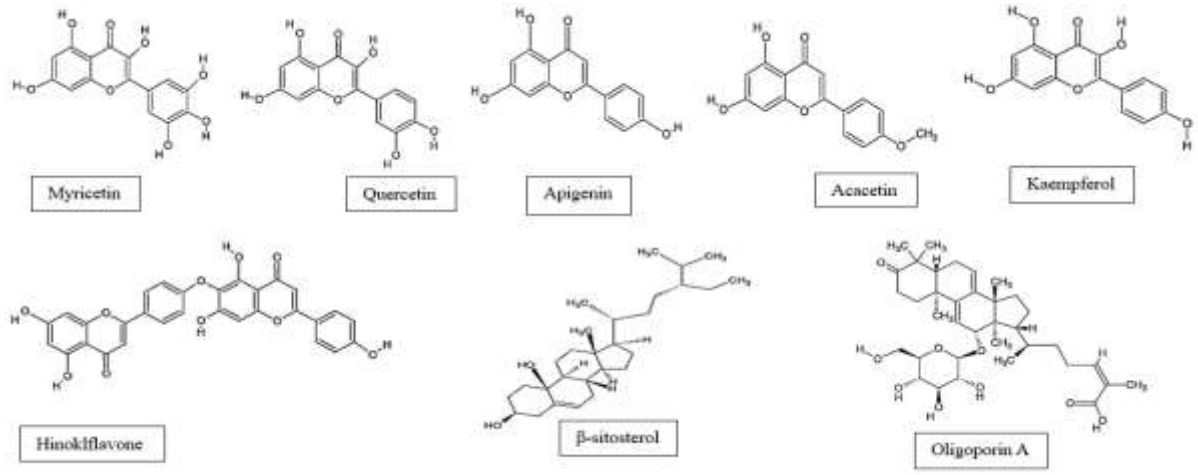
Figure 2: Anticoagulative mechanism of Phytocompounds of CAMs by inhibition coagulation factors, fibrinolytic activity, and thrombolytic (plasmin-like) activity.

4.2 Anticoagulant activity by plasma defibrinogenation

Hyperfibrinogenaemia (plasma fibrinogen > 400 mg/dL) elevates thrombosis and other CVDs risk. Several plants derived fibrinogen degrading enzymes (α and β fibrinogenase) cleave the *Aα*,[39,40,41] and *αβ* chains of fibrinogen,[31,38] lowering circulating fibrinogen and effectively defibrinogenation plasma.

4.3 Anti-platelet activity inhibiting blood coagulation

In-vitro antiplatelet activity has been shown by Oligoporin A (~631 Da) extracted from an edible mushroom *Oligoporus tephroleucus* elevates intraplatelet cyclic adenosine monophosphate (cAMP) / cyclic guanosine monophosphate (cGMP), suppresses collagen-induced suppress extracellular signal-regulated kinase 2 (ERK2) phosphorylation and prevents fibrinogen binding to integrin IIb/IIIa, potently inhibiting collagen-induced aggregation of platelets without affecting thrombin- or adenosine diphosphate (ADP)-driven pathways.[42] Fungal extracts (e.g., *Phellinus baummii* methanol extract; an edible mushroom used as folk medicine to fight various diseases) similarly raise cAMP and concomitantly inhibit ERK2/ c-Jun N-terminal kinase 1 (JNK1) phosphorylation to dose-dependently block collagen, thrombin and ADP-induced platelet clumping.[43] In an in vitro study by an ethyl acetate extract of *Caesalpinia sappan L.* inhibited human platelet activation by maintaining a balance between Thromboxane A_2 (TXA2) and



Prostacyclin (PGI2) levels.[44]

Figure 3: Chemical structure of the anticoagulative phytochemical compounds as source of CAMs. The figures were drawn using ChemSketch software.[45]

4.4 Clot-busting activity (thrombolysis)

Small subset of phytoconstituents exhibits direct fibrinolytic or plasminogen-activating activity. Plant-derived fibrinolytic serine proteases (e.g., nattokinase-like enzymes and lumbrokinases) and flavonoids such as rutin have demonstrated in-vitro clot lysis, albeit with wide variability in potency.[46] To date, most data are limited to test-tube assays; rigorous preclinical thrombolysis models are needed to validate these "clot-buster" phytopharmaceuticals

Table 1: List of some CAMs and their components actively acting on blood coagulation[47]

Plant Name	Parts used/Type of extract / Active compounds	Study Type	Mechanism of Anticoagulation	References
Allium sativum	Ethanolic extract of aged garlic	*In-vitro*	Inhibited binding of fibrinogen to GP IIb/IIIa and increased level of cAMP.	*[48]*
Cinnamomum cassia	Eugenol and coniferaldehyde	*In-vitro*	Antiplatelet activity by inhibition of arachidonic acid, epinephrine-induced platelet aggregation	*[49]*
Curcuma aromatic	CAP-II (12.4 kDa serine protease)	*In-vitro*	Hydrolyses *Aα* followed by *Bβ* and *γ* subunits of fibrinogen	*[50]*

Petroselinum crispum L.	Polyphenols	*In-vitro and In-vivo*	Decreases platelet aggregation, increased tail bleeding time.	*[51]*
Rhododendron brachycarpam	Hyperoside	*In-vitro and In-vivo*	Prolongs APTT and PT of platelet-poor plasma Inhibits thrombin-and collagen-induced platelet aggregation	*[52]*
Solanum tuberosum	StSBTc-3 (Subtilisin type serine protease),72kDa	*In-vitro*	Hydrolyses *Bβ* followed by *Aα* and γ subunits of fibrinogen inhibits platelet aggregation.	*[53]*
Zingiber officinale	6-gingerol and 6-shogaol	*In-vitro*	Inhibition of arachidonic acid medicated activation of platelets.	*[54]*

Abbreviations: AA, Arachidonic acid; APTT, activated partial thromboplastin time; BT, bleeding time; CT, coagulative time; PT, prothrombin time; RT, r- calcification time; TT, thrombin time.

5. PHARMACOKINETICS OF NOVEL ORAL ANTICOAGULANTS (NOACs)

The study of drug absorption, distribution, metabolism, and excretion, known as Pharmacokinetics (PK), determines the clinical use and safety, and efficacy of novel oral anticoagulants (NOACs). The individual NOACs within this therapeutic group show different pharmacokinetic properties that affect their prescribed doses and monitoring needs, and treatment suitability across different patient groups. A strong grasp of anticoagulant pharmacokinetic features becomes necessary to enhance treatment results, along with reducing unfavourable consequences.[55]

5.1 Absorption

The extent and speed at which drugs are absorbed into the body after oral consumption determine how quickly and strongly the anticoagulant effect will begin. The absorption properties of NOACs are favourable, but each drug shows different absorption patterns. The prodrug dabigatran etexilate needs hydrolysis to become active dabigatran and achieves only a 6–7% oral bioavailability rate because it requires an acidic environment for absorption.[56] Differentiating Factor Xa inhibitors from dabigatran etexilate reveals their better and more exact absorption ability because rivaroxaban reaches excellent oral bioavailability exceeding 80% with food intake, and apixaban and edoxaban display food-independent absorption characteristics.[57,58] The absorption variability between patients depends on gastrointestinal transit duration and *P*-glycoprotein transporter interactions with other medications, which affect precise anticoagulation control in clinical practice.

5.2 Distribution

NOACs are distributed throughout different body compartments following systemic absorption, which influences their anticoagulant effects and drug elimination time, and drug-drug interactions. The majority of dabigatran stays within plasma and extracellular fluid spaces while showing moderate protein binding. The plasma protein binding of Factor Xa inhibitors reaches high levels with rivaroxaban at ~92–95% and apixaban at ~87%, and edoxaban at ~55%.[57,58,59] The population pharmacokinetic analysis of apixaban demonstrates that body weight and renal function affect drug distribution, but doctors do not need to modify treatment doses.[60] The distribution properties of anticoagulant medications need thorough evaluation in clinical settings, especially for patients who have extreme body weights or critical illnesses, which modify fluid volumes and protein levels.

5.3 Metabolism

Metabolic extent and pathways determine how NOACs are cleared from the body while affecting drug interactions and appropriate patient selection for hepatic impairment cases. Most of the dabigatran passes through the kidneys without change as it undergoes minimal hepatic metabolism.[56] Factor Xa inhibitors demonstrate different levels of hepatic metabolism because rivaroxaban and apixaban depend mainly on CYP3A4 enzyme activity.[57,58] Edoxaban's hepatic metabolism remains minimal compared to its renal elimination process, even though the drug shows activity with P-glycoprotein.[59] The clinical significance of these metabolic pathways becomes important because strong P-glycoprotein or CYP3A4 inhibitors or inducers can substantially modify NOAC plasma levels, which affects both treatment effectiveness and bleeding susceptibility.[55] Patients taking NOACs need hepatic function assessments both at baseline and periodically, especially when they have liver disease as a comorbid condition.

5.4 Excretion

The elimination process of NOACs happens through the kidneys and liver, which affects how long the drugs stay in the body and how often patients need to take them, and how much the drugs build up in the system. Renal function plays a vital role in determining dabigatran elimination because the drug is primarily eliminated through the kidneys by

approximately 80%.[56] The elimination of rivaroxaban and apixaban, and edoxaban occurs through combined renal and hepatic pathways, although rivaroxaban is eliminated through the kidneys at a rate of 35%,[57] and apixaban through the kidneys at a rate of 27%.[58] The renal elimination of edoxaban reaches 50%, so healthcare providers need to adjust the medication dose for patients with renal impairment.[59] The monitoring of renal function needs to be done promptly when prescribing NOAC therapy because elderly patients, along with those who have comorbidities that affect clearance, require special attention.[61] Patients with impaired renal function taking NOACs show higher bleeding risks according to data from ROCKET AF and other clinical trials. New research indicates that upcoming Factor Xa inhibitors demonstrate optimized elimination capabilities between the kidneys and liver, which leads to enhanced safety, together with superior performance.[62]

6. PHARMACODYNAMICS OF NOVEL ORAL ANTICOAGULANTS (NOACs)

Drug effects result from the analysis of drug concentration levels at the site of action through Pharmacodynamics (PD). The pharmacodynamic properties of novel oral anticoagulants (NOACs) remain essential because they determine both therapeutic effectiveness and safety outcomes and bleeding risks, and treatment strategies.[63] The different NOACs work toward anticoagulation, yet possess unique pharmacodynamic characteristics that determine their appropriate clinical use.

6.1 Mechanism of Action

NOACs function by blocking particular serine proteases, which play essential roles in the coagulation cascade. The anticoagulant effect of dabigatran arises from its direct binding to the thrombin Factor IIa active site, where it blocks fibrinogen cleavage into fibrin, thereby preventing clot formation.[63] Through its mechanism, dabigatran stops thrombin from activating platelets and prevents the coagulation amplification process. The deep, narrow catalytic pocket of thrombin creates an environment that enables strong dabigatran molecule binding.

Rivaroxaban and apixaban and edoxaban, and betrixaban function as Factor Xa inhibitors by targeting this enzyme, which transforms prothrombin into thrombin.[64] The open hydrophobic active site of Factor Xa enables specific and potent inhibitor binding because of the molecular design of these inhibitors.[65] The agents reduce thrombin generation upstream to stop clot formation while leaving preformed thrombin unaffected, thus achieving better control of anticoagulation and haemostasis.

6.2 Dose-response Relationships

The anticoagulant properties of NOACs depend on drug concentration levels, which directly correspond to plasma drug measurements. The maximum anticoagulant effects of dabigatran occur between one to three hours after administration because of its fast absorption and direct thrombin blocking mechanism.[63] The anticoagulant characteristics of rivaroxaban show a fast onset-offset at a single daily dose, yet its plasma concentration and anticoagulant action remain steady through two daily apixaban dosing intervals.[64] Edoxaban maintains optimal therapeutic outcomes while minimising bleeding risks because of its single daily administration. The knowledge of dose-response profiles becomes essential because it helps when adjusting doses for patients with renal impairment and when planning perioperative management.

3.3 Biomarkers for Anticoagulant Effects

The monitoring of NOACs does not require regular laboratory tests, but pharmacodynamic biomarkers prove essential during clinical crises or specific situations. The dilute thrombin time (dTT) and ecarin clotting time (ECT) provide reliable testing for anticoagulant activity measurement of dabigatran.[66,67] The activated partial thromboplastin time (aPTT) shows prolonged results yet proves non-specific for detection. Medical professionals should use drug-specific anti-Factor Xa assays to measure Factor Xa inhibitors.[68] The prothrombin time (PT) test may become longer when patients take rivaroxaban, but the test sensitivity changes based on which reagents are used, particularly for apixaban and edoxaban. The availability of these assays facilitates quick clinical choices during urgent surgical operations and bleeding emergencies, and overdose situations.

6.4 Therapeutic Windows and Monitoring Needs

NOACs offer broader therapeutic margins than traditional anticoagulants because they provide effective thromboprophylaxis without requiring regular coagulation monitoring tests.[62] Some medical situations require testing of anticoagulant effects. Major bleeding requires the use of reversal agents, including idarucizumab for dabigatran treatment and andexanet alfa for Factor Xa inhibitor patients. Emergency surgery, together with trauma and severe renal dysfunction and extreme body weights, and potent drug interactions, requires immediate monitoring or pharmacodynamic assessment.[69] The accumulation of NOAC drugs becomes more significant in patients with declining renal function because it raises the risk of bleeding.[66] The evaluation of individual patient risk factors enables safer anticoagulation practices, particularly when treating elderly and frail patients.[70]

7. CLINICAL APPLICATIONS AND DOSING CONSIDERATIONS

The clinical utility of novel oral anticoagulants (NOACs) has significantly transformed anticoagulation strategies for a wide range of thromboembolic conditions. Their predictable pharmacokinetics, fixed dosing, fewer interactions, and improved safety profiles over warfarin have simplified both outpatient and inpatient anticoagulant management.

7.1 Indications: Atrial Fibrillation, Deep Vein Thrombosis, Pulmonary Embolism

NOACs receive approval for stroke prevention with systemic embolism protection in non-valvular atrial fibrillation (AF) patients and for treating and preventing venous thromboembolism (VTE) that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The RE-LY and ROCKET AF and ARISTOTLE, and ENGAGE AF-TIMI 48 trials demonstrated that NOACs compare favourably to warfarin therapy by showing non-inferiority or superiority while reducing intracranial haemorrhage occurrences. These medications offer fast onset and simplified administration methods, which do not require bridging anticoagulation or routine INR monitoring, thus making them preferred choices in these applications. The reduced number of food and drug interactions leads to better patient adherence, which results in improved therapeutic consistency.

7.2 Standard Dosing vs. Individualized Dosing

The standard dosage of NOAC drugs originates from their phase III clinical trial results. The standard dose of dabigatran is 150 mg twice daily, while rivaroxaban requires 20 mg once daily with meals to maximise its absorption. Patients who are aged 80 years or older or have a body weight below 60 kg or serum creatinine levels at 1.5 mg/dL or higher should take apixaban at a reduced dose of 2.5 mg twice daily. The recommended dose of edoxaban stands at 60 mg once daily, yet patients with moderate renal impairment or body weight ≤60 kg need to take 30 mg daily.

The convenience of fixed dosing remains limited because it does not work well for every patient. When treating patients who have renal or hepatic impairment, or advanced age, or use CYP3A4 or *P*-glycoprotein modulators, it becomes necessary to adjust drug doses for each patient. The assessment of renal function requires creatinine clearance testing, above measuring serum creatinine alone in these situations. The management of bleeding risks requires either a reduction in dosage or a change in medication, or more regular monitoring to maintain therapeutic effectiveness.

7.3 Special Populations: Elderly, Renal Impairment, Liver Disease Patients

The use of NOACs provides advantages to elderly patients through their lower intracranial haemorrhage risk and simpler administration compared to warfarin. The natural changes in renal clearance, together with the drug metabolism of elderly patients, require physicians to constantly review treatment dosages. The combination of safety and effectiveness proves optimal for apixaban 2.5 mg twice daily administration in this patient group when specific individual criteria apply. The selection process and dosage determination of NOACs heavily depend on renal function assessment. The majority of dabigatran (80%) is eliminated through renal pathways, so patients with moderate-to-severe renal dysfunction need either substantial dose reductions or must avoid the medication altogether. The renal clearance of Edoxaban and rivaroxaban remains low, but doctors must modify dosages when creatinine clearance reaches specific, defined levels. The necessity for continuous renal function monitoring exists to prevent drug accumulation, which leads to elevated bleeding risk during the entire treatment duration.

Medical professionals should avoid prescribing rivaroxaban and apixaban to patients with hepatic impairment who have Child-Pugh B or C liver disease severity. The agents undergo significant hepatic metabolism, which leads to worsened coagulation problems and potential drug toxicity. Individual risk-benefit assessments need to be performed for this population because NOAC treatment should be avoided or used only with extreme caution.

8. CHALLENGES AND LIMITATIONS OF NOACS

The anticoagulation therapy has advanced significantly due to NOACs which provide better pharmacokinetic predictability and fixed dosing schedules and fewer drug interactions compared to vitamin K antagonists yet crucial clinical challenges remain unresolved. The understanding and acknowledgment of such limits are crucial when employing anticoagulants to protect patient safety in challenging patient populations.

8.1 Bleeding Risk

Bleeding stands as the principal and most severe adverse effect that occurs during NOAC therapy. The risk of intracranial haemorrhage with NOACs remains lower than warfarin, yet gastrointestinal bleeding, together with mucosal bleeding and bleeding in elderly or renally impaired patients, continues to pose significant concerns. The bleeding risk of each patient requires consideration during clinical decision-making because it depends on their age and renal function, as well as their comorbidities and antiplatelet agent use. Healthcare professionals should exercise clinical discretion regarding NOAC prescriptions to vulnerable patients despite available risk assessment methods.

8.2 Limited Antidote Access

Idarucizumab and andexanet alfa serve as reversal agents that help address safety concerns during major bleeding or urgent surgical procedures. The real-world application of these antidotes is restricted because they are either too expensive or not accessible in numerous healthcare facilities. Physicians often need to use general supportive measures or non-specific agents that show inconsistent effectiveness because reversal agents are unavailable. Healthcare facilities must enhance their availability of reversal strategies to improve safety throughout different healthcare settings.

8.3 Drug Interactions

The use of NOACs leads to fewer drug and dietary interactions in comparison to warfarin, but patients still experience important drug interactions. The anticoagulant medications known as NOACs function as substrates of P-glycoprotein transporters and cytochrome P450 enzymes. The combination of NOACs with strong inhibitors or inducers of P-glycoprotein transporters and cytochrome P450 enzymes leads to changes in plasma concentrations, which either heighten bleeding risks or diminish anticoagulant effects. The risk of treatment outcome modification becomes significant when polypharmacy patients fail to detect drug interactions.

8.4 Limitations in Special Populations

The clinical outcomes of NOACs in specific groups of patients currently lack clear evidence. Advanced renal or hepatic dysfunction patients face increased toxicity risk because their drug clearance functions poorly, and their drug levels build up in their bodies. The available evidence regarding NOACs in pregnant individuals, as well as paediatric patients and patients at the extremes of body weight, remains scarce. The assessment of bleeding risks and thrombotic protection should be done carefully in cancer patients who have gastrointestinal malignancies. The assessment and monitoring of these patient groups need to be personalised and intensive.

Research now supports the use of NOACs through more specific and individualised prescribing practices. Medical choices based on pharmacogenomic testing combined with individualized risk evaluation show promise for improved clinical therapy in the upcoming years. New research proves that a combination treatment from several medical specialists reduces chemical risks when performing a complete drug evaluation of complex patients using clinical anticoagulant therapies.[71]

9. CHALLENGES AND LIMITATIONS OF CAMs AS ANTICOAGULANTS

9.1 Production of authenticated CAMs

Despite growing demand, only a small fraction of CAMs products undergo rigorous authentication processes. This scarcity is driven by limited access to certified cultivation sites and a lack of standardized quality-control laboratories. Consequently, many manufacturers rely on loosely defined sourcing, which undermines both safety and consumer confidence.

9.2 The optimal dosages for herbal therapies

Dose-finding studies are scarce, and most recommendations are extrapolated from traditional use rather than evidence-based trials. Without stratification by BMI, age, organ function or comorbidities, patients may receive subtherapeutic or potentially harmful doses. Personalized dosing algorithms and well-designed pharmacokinetic studies are urgently needed to inform safe prescribing.

9.3 Understanding of the potential benefits and risks

While anecdotal and in vitro data suggest promising effects, robust clinical trials are few and far between. Many phytochemicals exhibit multiple mechanisms of action, making it difficult to predict both efficacy and off-target toxicities. Comprehensive safety profiling—including long-term surveillance—is essential to balance therapeutic advantages against possible adverse events.

9.4 Authentication of raw materials

Adulteration, misidentification, and substitution with related species are common when supplier verification is lax. Without chemical fingerprinting, the active-constituent profile can vary dramatically, compromising reproducibility. Implementing standardized authentication protocols at the harvest and processing stages would stabilize product quality.

9.5 Dearth of information on herb–drug interactions

Few studies have systematically evaluated how common botanicals influence cytochrome *P450* enzymes, transporters, or coagulation pathways. This knowledge gap raises the specter of unexpected potentiation or attenuation of conventional drugs. Rigorous in vivo and clinical interaction trials are needed to define safe co-administration guidelines.

9.6 Lack of essential researches

Innovative partnerships are rare, and funding streams often favor single-entity projects over multidisciplinary consortia. Regulatory hurdles—such as varying approval pathways across regions—further complicate market entry.

Strengthening networks that bridge traditional knowledge holders, scientists, and industry would accelerate product development and global distribution.

10. RECENT ADVANCES AND FUTURE DIRECTIONS

Novel oral anticoagulants (NOACs) continue to evolve, with current research focusing on improving their safety, effectiveness, and individualization. Recent developments span from enhanced reversal strategies to new therapeutic targets and precision-guided dosing models.

10.1 Development of Reversal Agents

The introduction of specific reversal agents represents a major advancement in NOAC therapy because they enable the treatment of emergency bleeding and surgical needs. The pharmaceutical industry created idarucizumab specifically to counteract the effects of dabigatran. The agent demonstrates strong binding properties to the drug, which enables quick and dependable reversal of its anticoagulant properties. The anticoagulant factor Xa inhibitors rivaroxaban and apixaban can be neutralised by andexanet alfa through its function as a decoy protein that binds to circulating anticoagulant molecules. Clinical trials and real-world applications demonstrate the effectiveness of these agents, which enhance the safety features of NOACs. The high costs and restricted availability in healthcare systems specifically hinders NOAC use extension mainly in low-resource or rural areas.

10.2 Newer NOACs Under Investigation

Upcoming investigations continue to develop next-generation anticoagulants that work against different parts of the coagulation mechanism beyond currently used medicines. The development of Factor XI and Factor XII inhibitors shows promise as they stop thrombosis formation without disrupting regular blood clotting processes. The new anticoagulant agents show potential to minimise bleeding complications better than existing NOACs. Newer oral anticoagulants having greater half-lives, together with once-weekly dosing protocols, undergo evaluation for better adherence and convenience. Researchers currently investigate extended-release formulations together with different delivery methods that mainly involve subcutaneous injections.

10.3 Personalized Anticoagulant Therapy

The medical field of anticoagulation therapy is moving toward individualised patient care. Pharmacometabonomics research allows medical professionals to predict how gene variations impact drug absorption and breakdown in patients. Future NOAC dose selection will benefit from genetic variants in the ABCB1 and CES1 genes, which affect drug plasma levels and treatment results. Artificial intelligence risk prediction models, together with patient-specific variables, combined with point-of-care coagulation tools, help create more personalized anticoagulant therapy. The innovations will help decrease adverse events and enhance the benefit–to–risk ratio of NOACs for various patient groups.

10.4 Multimodal Screening Technologies in CAMs components

High-throughput screening, microarray chip assays, fluorescence sensor platforms, and computational biology have accelerated the rapid identification and validation of anticoagulant and antiplatelet phytoconstituents, reducing candidate selection cycles from months to weeks.[72] Concurrently, bioassay-guided fractionation techniques employing multidimensional chromatography and mass spectrometry allow for precise isolation of active components, such as specific flavonoids and phytosterols, enhancing reproducibility and efficacy profiling.[73]

10.5 Newer modified drug-delivery systems

Nano-emulsions (ultra-diluted medicines), plant-derived exosome-like nanoparticles-have emerged to overcome poor bioavailability and rapid metabolism of phytochemical actives. Parallel clinical studies of standardized extracts like maritime pine bark and ginsenoside-rich ginseng preparations, have shown significant improvements in endothelial function, reductions in platelet aggregation, and favourable safety profiles in small-scale human trials.[74]

11. CONCLUSION

NOACs have reshaped anticoagulation therapy by providing predictable pharmacokinetic and pharmacodynamic profiles, fixed dosing regimens, minimized drug interactions, and enhanced patient convenience over vitamin K antagonists. A thorough understanding of their absorption, distribution, metabolism, excretion, and target-specific inhibition of thrombin or Factor Xa is essential for safe and effective clinical practice. These agents exhibit rapid onset, short half-lives, and broad therapeutic windows that often obviate frequent monitoring; however, individual variability–stemming from age, renal/hepatic function, genetic polymorphisms, body weight, and concomitant medications-necessitates careful evaluation by clinicians, especially in elderly, oncologic, and organ-impaired patients. Emergency management has improved with idarucizumab and andexanet alfa, but broader access to affordable and accessible reversal agents remains a priority. Parallel exploration of complementary and alternative medicines, including authenticated herbal extracts, advanced bioassay-guided fractionation, nano-formulations, and innovative delivery

systems—has revealed promising antithrombotic, antiplatelet, and fibrinolytic effects. Recent advancements in high-throughput screening, computational biology, microarray assays, and plant-derived exosome-like nanoparticles have accelerated the identification and delivery of potent phytoconstituents, while early-phase clinical validations underscore their translational potential. Nonetheless, challenges persist in raw material authentication, robust dose–response and herb–drug interaction studies, and regulatory harmonization via international consortia like IRCH and WHO initiatives. Looking ahead on innovations in pharmacogenomics, AI-driven decision support, and advanced PK/PD modeling offer individualized anticoagulation strategies that account for patient-specific physiology, comorbidities, and risk factors. The development of next-generation agents targeting Factor XI and XII promises thromboprophylaxis with reduced bleeding risks. Future research must prioritize long-term safety surveillance, optimized dosing in special populations, expanded access to reversal techniques and monitoring tools, and multidisciplinary collaboration to integrate synthetic and phytopharmaceutical approaches. By combining these strategies, the next generation of evidence-based antithrombotic therapies can be realized, advancing precision anticoagulation and improving outcomes across diverse clinical settings.

REFRENCES

1. WHO. Cardiovascular diseases [Internet]. World Health Organisation. 2025. Available from: https://www.who.int/health-topics/cardiovascular-diseases
2. Prabhakaran D, Jeemon P, Sharma M, Roth GA, Johnson C, Harikrishnan S, et al. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6(12):e1339–51.
3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42(5):373–498.
4. Lip GY, Banerjee A, Boriani G, Chiang C, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154(5):1121–201.
5. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. EP Europace. 2021;23(10):1612–76.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
10. Cuker A, Burnett A, Triller D, Crowther M, Ansell J, Van Cott EM, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94(6):697–709.
11. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.
12. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380(14):1326–35.
13. Masini M, Toma M, Spallarossa P, Porto I, Ameri P. Direct oral anticoagulants for cancer-associated venous thromboembolism. Curr Oncol Rep. 2023;25(9):979–87.
14. Fawzy AM, Lip GY. Pharmacokinetics and pharmacodynamics of oral anticoagulants used in atrial fibrillation. Expert Opin Drug Metab Toxicol. 2019;15(5):381–98.
15. Ragia G, Manolopoulos VG. Pharmacogenomics of anticoagulation therapy: The last 10 years. Pharmacogenomics. 2019;20(16):1113–17.
16. Manzoor BS, Lee TA, Sharp LK, Walton SM, Galanter WL, Nutescu EA. Real-world adherence and persistence with direct oral anticoagulants in adults with atrial fibrillation. Pharmacotherapy. 2017;37(10):1221–30.
17. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med. 2007;146(3):211–22.
18. Siegel DM, Garcia DA, Crowther MA. How I treat target-specific oral anticoagulant–associated bleeding. Blood. 2014;123(8):1152–8.

19. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products. 2020 Mar 12;83(3):770–803.
20. Cordier W, Cromarty AD, Botha E, Steenkamp V. Effects of selected South African plant extracts on haemolysis and coagulation. Human & Experimental Toxicology. 2011 Feb 4;31(3):250–7.
21. Li J, Liang Q, Sun G. Interaction between Traditional Chinese Medicine and Anticoagulant/Antiplatelet Drugs. Current Drug Metabolism. 2019 Oct 4;20(9):701–13.
22. Memariani Z, Moeini R, Hamedi SS, Gorji N, Mozaffarpur SA. Medicinal plants with antithrombotic property in Persian medicine: a mechanistic review. Journal of Thrombosis and Thrombolysis. 2017 Nov 9;45(1):158–79.
23. Sen S, Chakraborty R. Revival, modernization and integration of Indian traditional herbal medicine in clinical practice: Importance, challenges and future. Journal of Traditional and Complementary Medicine. 2017 Apr;7(2):234–44.
24. WHO. 2014-2023 WHO Traditional Medicine Strategy [Internet]. Available from: https://iris.who.int/bitstream/handle/10665/92455/9789241506090_eng.pdf
25. Mackman N, Bergmeier W, Stouffer GA, Weitz JI. Therapeutic strategies for thrombosis: new targets and approaches. Nat Rev Drug Discov. 2020;19(5):333–52.
26. Gross PL, Weitz JI. New antithrombotic drugs. Clin Pharmacol Ther. 2009;86(2):139–46.
27. Bauer KA. Pros and cons of new oral anticoagulants. Hematology Am Soc Hematol Educ Program. 2013;2013(1):464–70.
28. Rose DK, Bar B. Direct oral anticoagulant agents: pharmacologic profile, indications, coagulation monitoring, and reversal agents. J Stroke Cerebrovasc Dis. 2018;27(8):2049–58.
29. Brummel-Ziedins KE, Whelihan MF, Gissel M, Mann KG. Hemostasis and thrombosis. Haemophilia. 2009;15:1118–25.
30. Ali AE, Becker RC. The foundation for investigating factor XI as a target for inhibition in human cardiovascular disease. J Thromb Thrombolysis. 2024;57(8):1283–96.
31. Gogoi D, Pal A, Chattopadhyay P, Paul S, Deka RC, Mukherjee AK. First Report of Plant-Derived β-Sitosterol with Antithrombotic, in Vivo Anticoagulant, and Thrombus-Preventing Activities in a Mouse Model. J Nat Prod. 2018;81(11):2521-30.
32. Gogoi D, Ramani S, Bhartari S, Chattopadhyay P, Mukherjee AK. Characterization of active anticoagulant fraction and a fibrin(ogen)olytic serine protease from leaves of Clerodendrum colebrookianum, a traditional ethno-medicinal plant used to reduce hypertension. J Ethnopharmacol. 2019;243:112099.
33. Guan Shixia, Yuan Zhongwen, Zhou Yubin, Yi Z, Ye Xiaoling, Bo H. Comparative studies on anti-thrombus and anti-coagulation effects of Hirudo of different species. Chinese Journal of Hospital Pharmacy. 2012 Jan 1;32(14):1093–6.
34. Lu PH, Kuo CY, Chan CC, Wang LK, Chen ML, Tzeng I-Shiang, et al. Safflower Extract Inhibits ADP-Induced Human Platelet Aggregation. Plants. 2021 Jun 11;10(6):1192.
35. Liu L, Ma H, Yang N, Tang Y, Guo J, Tao W, et al. A Series of Natural Flavonoids as Thrombin Inhibitors: Structure-activity relationships. Thrombosis Research. 2010 Nov;126(5):e365–78.
36. Bijak M, Ziewiecki R, Saluk J, Ponczek M, Pawlaczyk I, Krotkiewski H, et al. Thrombin inhibitory activity of some polyphenolic compounds. Medicinal Chemistry Research. 2013 Oct 16;23(5):2324–37.
37. Gogoi D, Arora N, Kalita B, Sarma R, Islam T, Ghosh SS, et al. Anticoagulant mechanism, pharmacological activity, and assessment of preclinical safety of a novel fibrin(ogen)olytic serine protease from leaves of Leucas indica. Scientific Reports. 2018 Apr 18;8(1).
38. Gogoi D, Jha S, Chattopadhyay P, Mukherjee AK. A simple, cost-effective, and rapid separation process for the isolation of anticoagulant active fraction from the fruit extract of Momordica charantia: Characterization of bioactive components and anticoagulant mechanism of active fraction in a mouse model. J Sep Sci. 2020;43(20):3902-12.
39. Choi JH, Dae Won Kim, Park SE, Choi BS, Kumar Sapkota, Kim SU, et al. Novel thrombolytic protease from edible and medicinal plant Aster yomena (Kitam.) Honda with anticoagulant activity: Purification and partial characterization. Journal of Bioscience and Bioengineering. 2014 Oct 1;118(4):372–7.
40. Choi JH, Sapkota K, Park SE, Kim S, Kim SJ. Thrombolytic, anticoagulant and antiplatelet activities of codiase, a bi-functional fibrinolytic enzyme from Codium fragile. Biochimie. 2013;95(6):1266-77.
41. Kim DW, Sapkota K, Choi JH, Kim YS, Kim S, Kim SJ. Direct acting anti-thrombotic serine protease from brown seaweed Costaria costata. Process Biochemistry. 2013 Feb;48(2):340–50.

42. Park JY, Oh WJ, Kim MJ, et al. Mechanism of anti-platelet activity of Oligoporus tephroleucus oligoporin A: involvement of extracellular signal-regulated kinase phosphorylation and cyclic nucleotide elevation. Platelets. 2012;23(5):376-85.
43. Kamruzzaman SM, Endale M, Oh WJ, et al. Antiplatelet activity of Phellinus baummii methanol extract is mediated by cyclic AMP elevation and inhibition of collagen-activated integrin-α(IIb) β_3 and MAP kinase. Phytother Res. 2011;25(11):1596-1603.
44. Chang Y, Huang SKH, Lu WJ, Chung CL, Chen WL, Lu SH, et al. Brazilin isolated from Caesalpinia sappan L. acts as a novel collagen receptor agonist in human platelets. Journal of Biomedical Science. 2013 Jan 25;20(1).
45. ACD Labs. ChemSketch Freeware [Internet]. ACD/Labs. Available from: https://www.acdlabs.com/resources/free-chemistry-software-apps/chemsketch-freeware/
46. Standeven KF, Ariens RA, Grant PJ. The molecular physiology and pathology of fibrin structure/function. Blood Rev. 2005;19(5):275-288.
47. Mukherjee AK, Chattopadhyay DJ. Potential clinical applications of phytopharmaceuticals for the in-patient management of coagulopathies in COVID-19. Phytother Res. 2022;36(5):1884-1913.
48. Allison GL, Lowe GM, Rahman K. Aged garlic extract inhibits platelet activation by increasing intracellular cAMP and reducing the interaction of GPIIb/IIIa receptor with fibrinogen. Life Sci. 2012;91(25-26):1275-80.
49. Kim SY, Yun-Choi HS. A comparative optical aggregometry study of antiplatelet activity of taxanes from Taxus cuspidata. Thromb Res. 2010;125(6):e281-284.
50. Shivalingu BR, Vivek HK, Priya BS, Soujanya KN, Swamy SN. Purification and characterization of novel fibrin(ogen)olytic protease from Curcuma aromatica Salisb.: Role in hemostasis. Phytomedicine. 2016;23(13):1691-98.
51. Agyare C, Appiah T, Boakye YD, Apenteng JA. Petroselinum crispum: a Review. Medicinal Spices and Vegetables from Africa. 2017;527–47.
52. Ku SK, Bae JS. Antithrombotic activities of wogonin and wogonoside via inhibiting platelet aggregation. Fitoterapia. 2014;98:27-35.
53. Pepe A, Frey ME, Munoz F, et al. Fibrin(ogen)olytic and antiplatelet activities of a subtilisin-like protease from Solanum tuberosum (StSBTc-3). Biochimie. 2016;125:163-70.
54. Liao YR, Leu YL, Chan YY, Kuo PC, Wu TS. Anti-platelet aggregation and vasorelaxing effects of the constituents of the rhizomes of Zingiber officinale. Molecules. 2012;17(8):8928-37.
55. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharmacokinet. 2013;52:69–82.
56. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014;53:1–16.
57. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet. 2019;58:1265–79.
58. Parasrampuria DA, Truitt KE. Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa. Clin Pharmacokinet. 2016;55:641–55.
59. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014;63(4):321–8.
60. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation. EP Europace. 2015;17(10):1467–507.
61. Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. Blood. 2019;133(5):425–35.
62. Pinto DJ, Smallheer JM, Cheney DL, Knabb RM, Wexler RR. Factor Xa inhibitors: next-generation antithrombotic agents. J Med Chem. 2010;53(17):6243–54.
63. Byon W, Sweeney K, Frost C, Boyd RA. Population pharmacokinetics, pharmacodynamics, and exploratory exposure–response analyses of apixaban in subjects treated for venous thromboembolism. CPT Pharmacometrics Syst Pharmacol. 2017;6(5):340–9.
64. Bradbury CA, McQuilten Z. Anticoagulation in COVID-19. Lancet. 2022;399(10319):5–7.
65. Connolly SJ, Milling TJ, Eikelboom JW. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. J Vasc Surg. 2017;65(1):279–80.

66. Favaloro EJ, Pasalic L, Curnow J, Lippi G. Laboratory monitoring or measurement of direct oral anticoagulants (DOACs): advantages, limitations and future challenges. Curr Drug Metab. 2017;18(7):598–608.
67. Testa S, Tripodi A, Legnani C, Pengo V, Abbate R, Dellanoce C, et al. Plasma levels of direct oral anticoagulants in real-life patients with atrial fibrillation: results observed in four anticoagulation clinics. Thromb Res. 2016;137:178–83.
68. Aronson JK. Biomarkers and surrogate endpoints. Br J Clin Pharmacol. 2005;59(5):491.
69. Van der Hulle T, Kooiman J, Den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320–8.
70. Scicchitano P, Tucci M, Bellino MC, Cortese F, Cecere A, De Palo M, et al. The impairment in kidney function in the oral anticoagulation era: a pathophysiological insight. Cardiovasc Drugs Ther. 2021;35:505–19.
71. Shih AW, Crowther MA. Reversal of direct oral anticoagulants: a practical approach. Hematology Am Soc Hematol Educ Program. 2016;2016(1):612–9.
72. Liu X, Chen L, Li L, Yan Y, Zhang H. Research Progress in In Vitro Screening Techniques for Natural Antithrombotic Medicines. Pharmaceuticals (Basel). 2025;18(2):137.
73. Subramani B, Sathiyarajeswaran P. Current update on herbal sources of antithrombotic activity-a comprehensive review. Egypt J Intern Med. 2022;34(1):26.
74. Mostafa RE, Ali DE, El-Shiekh RA, et al. Therapeutic applications of natural products in the management of venous diseases: a comprehensive review. Inflammopharmacology. 2025;33(4):1673-1712.