

Introduction

Chapter 1

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1.1 Introduction

For well over a century, the allopathic healthcare industry has dedicated significant efforts to combat degenerative diseases, encompassing conditions like cardiovascular disorders, metabolic syndromes, cancer, inflammatory ailments, and neurodegenerative diseases such as Alzheimer's, Parkinson's, Hodgkin's, and various others. While substantial progress has been achieved in disease diagnosis, the ongoing struggle to enhance the quality of human life and provide effective treatments for these ailments persists. Unfortunately, many of these diseases lack precise and side-effect-free therapeutic solutions. Currently, the primary recourse available consists of a lengthy roster of prescription medications, which may offer symptom relief but often come at the cost of undermining the body's immunity and overall quality of life (Kodali G, 2013).

Herbal medicines represent the amalgamation of centuries of healing wisdom from traditional medical practitioners. These natural remedies have garnered significant attention in the developed world due to their perceived safety, efficacy, and minimal side effects, making them increasingly popular for primary healthcare. Moreover, herbal medicines have shown promise in addressing age-related conditions such as osteoporosis, memory loss, and immune disorders, where modern medicine options are limited. Despite India's rich traditional knowledge and vast biodiversity, the country's share in the global herbal medicine market remains modest, primarily due to the export of raw extracts and unprocessed drugs (Kamboj, 2000).

The World Health Organization (WHO) has officially defined traditional medicine, including herbal remedies, as healing practices that predate the rise and proliferation of modern medicine, with many of these practices still in use today (WHO, 2019). WHO has been actively supporting programs that aim to integrate medicinal plants into conventional healthcare systems, particularly in developing countries where they are affordable, accessible, and deeply rooted in the local culture. In contrast, the development of synthetic drugs is not only costly but also time-consuming, often requiring investments ranging from 0.5 to 5 million dollars for a new product. Conversely, many medicinal herbs form the backbone of traditional medicine across the globe, offering cost-effective solutions, and their structurally diverse components hold the potential for novel therapeutic compounds.

Therefore, there is a compelling need to explore new medicinal plants for the development of safer, more affordable, and effective drugs (Almeida et al., 2001).

Traditional preparations involve various elements, including minerals, medicinal plants, and organic substances. Herbal drugs are a subset of traditional medicines, primarily relying on medicinal plant preparations for remedies. Ancient texts like the Rigveda, Charak Samhita, Athar Veda, and Sushruta Samhita provide the earliest documented evidence of herbal medicine use, dating back approximately 5000 years. These herbal remedies have evolved from the rich traditions of ancient civilizations and scientific practices.

In the absence of modern synthetic drugs, humans historically depended on medicinal herbs for treating and preventing diseases. The utilization of medicinal herbs for healing purposes has been an integral part of the history of ancient civilizations (Shahriar et al., 2014). Herbal medicine emphasizes the rejuvenation of bodily systems, disease prevention, and the promotion of a healthy, extended lifespan (Mahe et al., 1978). Medicinal herbs play a crucial role in traditional medicine practices globally, primarily in developing countries, due to their affordability, accessibility, and wisdom passed down through generations (Prasad et al., 2013). At present, herbal medicine maintains its popularity not only in many developing nations but is also rapidly gaining ground in industrialized countries. It has been reported that a significant proportion of medical practitioners in France and Germany, estimated at around 70%, routinely recommend herbal remedies to their patients. Additionally, there has been a remarkable surge in the number of patients seeking herbal treatments, as this figure continues to grow exponentially (Cragg et al., 1997). Globally, it is anticipated that approximately 80% of the world's population employs herbal therapies, with rates in developing countries potentially reaching as high as 95% (Tilburt and Kaptchuk, 2008). In China, traditional herbal medicine accounts for a substantial portion, ranging from 30% to 50%, of the total drug consumption. In nations like Ghana, Mali, Nigeria, and Zambia, herbal medicines serve as the primary choice for home-based initial treatment, making up 60% of such cases. Moreover, in Europe, North America, and other developed regions, more than half of the population has, at some point in their lives, explored herbal medicinal approaches (Gunjan et al., 2015). Notably, in locations like San Francisco, London, and South Africa, 75% of individuals affected by HIV/AIDS turn to herbal formulations for support. In Canada and Germany, an impressive 70% to 90% of the population has embraced herbal medicines at least once in their lifetime. In the United

States, an estimated 158 million adults have incorporated herbal remedies into their healthcare practices, and this trend is on the rise. In total, the global market for herbal medicines presently exceeds US\$60 billion annually and is experiencing steady growth (Robinson and Zhang 2011; Gunjan et al., 2015).

What's particularly intriguing is that the adult population appears to be increasingly open to a balanced approach, combining both conventional and herbal medicines. This demographic, which tends to experience a higher incidence of chronic diseases, often faces discouraging long-term side effects associated with complex conventional drug therapies. In contrast, herbal medicines offer a treatment option with a notable absence of side effects, even with prolonged use. Given these distinctive qualities, herbal medicine has garnered widespread interest and is enjoying a fast-paced global acceptance (Khan & Ahmad 2019). To stop bleeding, or hemostasis, the balance between clot creation and clot breakdown must be precisely maintained. Hemostasis disorders represent a group of medical conditions characterized by an imbalance in the body's ability to regulate blood clotting. Hemostasis, a critical physiological process, maintains vascular integrity and prevents excessive bleeding in response to injury. When this intricate system becomes disrupted, it can lead to a range of bleeding or thrombotic disorders. Thrombosis occurs when a clot forms inside a vessel instead of where the vessel wall has been breached by injury. Thrombosis can happen in veins or arteries. Most heart attacks and strokes are caused by arterial thrombosis, but deep vein thrombosis—a type of venous thrombi in the veins—can break off and travel to the lungs, resulting in a pulmonary embolism. Thus, it should come as no surprise that enormous efforts have been made to create anticoagulants and antiplatelet medications, as well as to better understand the pathophysiology of thrombosis, to prevent and cure this frequent and potentially fatal illness (Mannucci & Tuddenham 2001).

1.2 Epidemiology:

Hemostasis disorders encompass a spectrum of conditions with varying prevalence across different populations. While some hemostatic disorders are relatively rare, others are more common. For example, hemophilia, an inherited bleeding disorder, has an estimated global prevalence of about 1 in 5,000 male births for hemophilia A and 1 in 30,000 male births for hemophilia B. Von Willebrand disease, another hereditary bleeding disorder, is the most common inherited bleeding disorder, affecting approximately 1% of the population (Beckman MG 2010).

In contrast, thrombotic disorders, such as deep vein thrombosis (DVT) and pulmonary embolism (PE), are more prevalent. DVT affects approximately 1 in 1,000 individuals annually, while PE occurs in up to 600,000 people in the United States each year. These conditions are influenced by various factors, including genetic predisposition, lifestyle, and environmental factors (Beckman MG 2010).

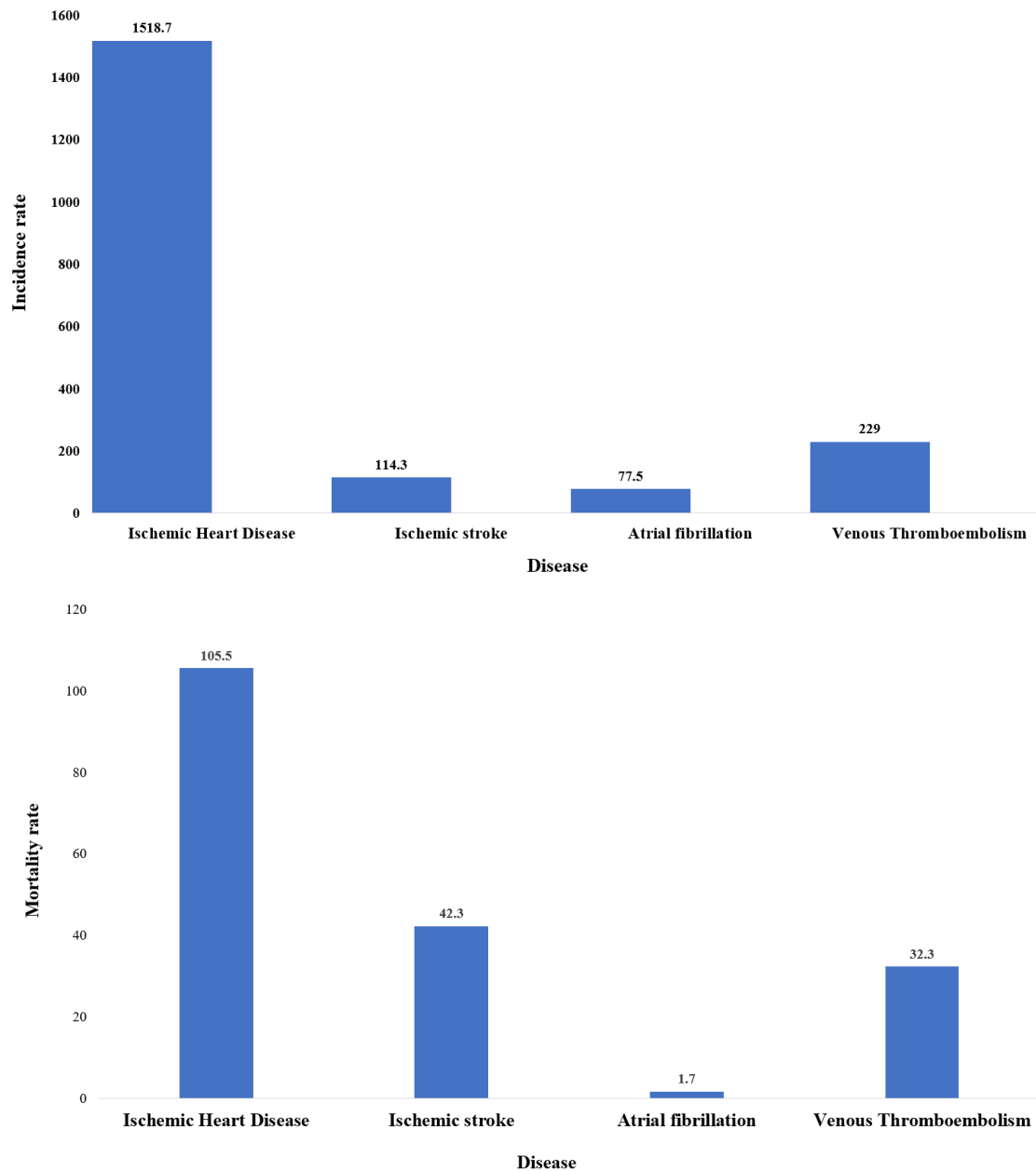


Figure 1.1: a) Incidence rate 1b) Mortality rate of thrombotic diseases (Wendelboe & Raskob 2016)

1.3 Etiology of Hemostasis:

The etiology of hemostasis disorders is multifaceted, often involving a combination of genetic, acquired, and environmental factors (Mannucci & Tuddenham 2001, Beckman et.al 2010).

1.3.1 Inherited or genetic factors

It plays a significant role in many hemostatic disorders. Mutations in genes encoding clotting factors, platelet receptors, or proteins involved in the coagulation cascade can lead to bleeding or thrombotic disorders. For example, hemophilia A and B result from mutations in the F8 and F9 genes, respectively.

1.3.2 Acquired factors

Acquired factors, such as liver disease, vitamin K deficiency, and medications, can also disrupt hemostasis. Liver dysfunction impairs the synthesis of clotting factors, while vitamin K deficiency affects the activation of these factors. Additionally, certain medications, such as anticoagulants and antiplatelet drugs, can alter the balance of hemostasis.

1.3.3 Environmental factors

Environmental factors, such as trauma, surgery, or immobility, may trigger hemostatic disorders. In the case of thrombotic disorders, conditions like obesity, smoking, and hormonal contraceptives can increase the risk of clot formation.

Understanding the epidemiology and etiology of hemostasis disorders is crucial for accurate diagnosis, risk assessment, and the development of effective treatment strategies, as these conditions have a significant impact on the overall health and quality of life of affected individuals.

1.4 Thrombotic Disease and its alternative herbal treatment:

Among all the disorders, thrombotic disease has the highest occurrence and poses a major threat to human life and health. Thrombosis incidence continues to show an increasing tendency. Research on thrombotic illness has emerged as one of the major areas of interest and focus in contemporary medicine in recent years. The prevention and treatment of this condition have benefited greatly from drug therapy. There are now only three primary categories of anti-thrombotic medications available on the market: thrombolytic, anticoagulant, and anti-platelet medications. These medications can be expensive and come with a higher risk of side effects. Therefore, there is a pressing need for clinical drug therapy

for this condition to produce an anti-thrombotic medication that is low-cost, safe, and efficacious. Certain vascular illnesses have thrombosis as their primary cause (Choi et al., 2015). Abnormal lipid metabolism has been linked to several cardiovascular and cerebrovascular disorders, high-fat hyperlipidemia, obesity, hypertension, atherosclerosis, coronary heart disease, myocardial infarction, and cerebral thrombosis. According to Devi and Sharma (2004), the primary causes are elevated levels of low-density lipoprotein cholesterol (LDL-C), decreased levels of high-density lipoprotein cholesterol (HDL-C), an increase in free radicals, and lipid peroxidation. The biomedical community has recently shown a growing interest in separating thrombolytic medicines and anti-thrombotic compounds—which are thought to be safer and more effective—from dietary and natural sources. Plants, minerals, and other dietary components may serve as alternative sources for the development of new thrombotic agents. Various scientific reports exhibit that the consumption of dietary anticoagulants, antioxidants, or phytochemicals with anticoagulant properties can ultimately reduce the risks of thrombotic disorders (Matsubara et.al, 2001; Guglielmone et.al., 2002).

India, having a rich tradition of folk medicine for centuries, has provided very simple but effective remedies to various ailments using plants and plant-derived compounds. Ancient literature mentions many herbal medicines for treating various diseases like Diabetes mellitus, rheumatoid arthritis, and cardiovascular diseases. We have also seen an increase in the popularity and use of natural remedies in developed countries, including herbs, herbal medicines, over-the-counter health foods, nutraceuticals, and herbal medicinal products. The use of herbal medicines is especially prevalent in primary health care and for many chronic diseases. But unfortunately, many potential plants in India lack scientific documentation.

Chemical principles from natural sources have become much simpler and have contributed significantly to the development of new drugs from medicinal plants. The valuable medicinal properties of different plants are due to the presence of several constituents i.e., saponins, tannins, alkaloids, phenols, flavonoids, terpenoids, etc. The numerous beneficial effects attributed to phenolic products have given rise to a new interest in finding botanical species with high phenolic and flavonoid content and their relevant biological activity.

The mechanism of herbal medicines in hemostasis involves various natural compounds and botanicals that can affect different aspects of the coagulation process. While the specific mechanisms can vary depending on the herbal remedy, some general mechanisms include

antiplatelet, anticoagulant, and fibrinolytic activities. These mechanisms can help regulate blood clotting and promote healthy hemostasis (Li et.al., 2015).

Here is a simplified explanation of these mechanisms:

Antiplatelet Activity: Some herbal medicines contain compounds that inhibit platelet aggregation. Platelets play a crucial role in the initial stages of blood clot formation. Herbal remedies with antiplatelet activity can reduce the risk of excessive clot formation. Curcumin has been shown to inhibit platelet-activating factor (PAF) -induced aggregation in human platelets, suggesting its potential as a natural anti-inflammatory and antiplatelet agent (Srivastava & Mustafa, 1984).

Anticoagulant Activity: Certain herbs contain natural anticoagulant compounds that interfere with the blood coagulation cascade. These compounds may inhibit the activation of clotting factors, thereby slowing down the clotting process. The inhibitory effect of resveratrol, a polyphenolic compound, on tissue factor expression in vascular cells. Tissue factor is an important initiator of the coagulation cascade. Resveratrol's ability to inhibit tissue factor expression suggests its potential anticoagulant properties and contributes to the cardiovascular benefits associated with moderate wine consumption (Pendurthi et.al, 1999).

Fibrinolytic Activity: Fibrinolysis is the process of breaking down clots. Some herbal medicines have fibrinolytic properties, which can help dissolve existing blood clots and prevent their excessive accumulation (Serrat et.al., 2022).

These mechanisms can be attributed to various herbal components, such as flavonoids, terpenoids, and other bioactive compounds found in plants. It's important to note that the effects of herbal medicines on hemostasis can vary, and their safety and efficacy should be carefully evaluated.

Several chemical groups found in plants can exhibit anticoagulant activity. One of the well-known chemical groups with anticoagulant properties is coumarins. Coumarins are natural compounds that interfere with the coagulation process by inhibiting vitamin K-dependent clotting factors (Hashim, 2017). Polyphenolic compounds (Teodosio Melo et.al., 2013, Bojić et.al., 2019) are known for their potential anticoagulation activity. These natural compounds can influence various aspects of the coagulation process (Huang et.al., 2003). Flavonoids (Chuluunbaatar et.al., 2021, Pouyfung & Sukati, 2021, Sahagun et.al., 2021, Guglielmone et.al., 2022), carotenoids (Teodosio Melo et.al., 2013), and polysaccharides (Mira et.al., 2017) are known to exhibit multiple biological activities, including antioxidant,

antiplatelet, anticoagulant, and antithrombotic effects. Researchers have demonstrated the anticoagulant activity of tannins, while some terpenoids are recognized for their antioxidant properties (Li et.al., 2014). Additionally, saponins are known to possess antiplatelet, anticoagulant, and fibrinolytic characteristics (Mosa, 2011).

The phenolic and flavonoid compounds provide hypolipidemic effect without restricting caloric intake and change in lifestyle. But the number of polyphenols present in our commonly consumed food is very low. Hence dietary supplements rich in polyphenols are recommended for achieving beneficial results. Evidence on the cholesterol-lowering properties of medicinal plants has been accumulating and several plants are useful in the treatment of hyperlipidemia such as Salicylates which are found in Willow Bark (Desborough & Keeling, 2017), Ginkgo Biloba (Diamond et. al., 2000), Allium sativum (Rashid et.al., 2014), Curcuma longa (Sreejayan & Rao, 1994), Zingiber officinale (Lantz et.al., 2012).

 [Review

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