Review

Therapeutic agents for the management of atherosclerosis from herbal sources: A computational approach

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Abstract: One of the most prevalent illnesses in the world, atherosclerosis has a significant role in the development of hypertension, stroke, myocardial localised necrosis, and several other cardiovascular conditions. The possible pathways associated with atherosclerosis include NF-kB, PPARs, PTX3, NO, LXR, Notch, shear stress, and HSPs. Oxidative stress, which is characterised by excessive oxidation and improper exclusion, is brought on by smoking, diabetes mellitus, hypertension, and high cholesterol. In a number of ways, including lowering the oxidation of low-density lipoproteins, cell proliferation, limiting the arrangement of foam cells, encouraging reverse cholesterol transport, and downregulating pro-atherogenic genes and inflammatory mediators, herbal plant-based antioxidant agents are useful in the management, targeting, and treatment of atherosclerosis. The pathogenesis, progression, role of oxidative stress, herbal medications, potential targets or biomarkers, and pathways of atherosclerosis are presented in this review work. Additionally, current research on the diagnosis, treatment, and management of atherosclerosis, primarily with regard to herbal medications, is presented.

Keywords: Atherosclerosis; progression; biomarkers; herbal drugs; linked pathways; oxidative stress; drug targets; computational approach

1. Introduction

A natural therapy approach can also help patients with cardiovascular diseases like atherosclerosis [1–3]. Atherosclerosis is known to be the cause of cardiovascular issues like peripheral vascular disease, myocardial ischaemia, heart failure, heart attacks, and strokes [1]. It is sometimes called the leading cause of death and morbidity worldwide. Inflammation, damage, and malfunction of endothelial cells in the heart are hallmarks of atherosclerosis. Plaque accumulation in the damaged area, arterial constriction, cholesterol buildup on the arterial wall, and monocyte adhesion to the endothelium are all consequences of endothelial injury [4,5]. This process causes chronic inflammation, which ultimately results in thrombosis or stenosis [5-8].

The most common and serious cardiovascular disease (CVD), also known as coronary artery disease (CAD), is atherosclerosis, which affects both the heart and the brain. This disease, which is the real cause of death, starts in childhood and manifests clinically in maturity. It progresses slowly. Epidemiological studies have connected specific factors to the progression of atherosclerosis [9,10]. Risk factors for CAD include alcohol consumption, mental health issues, obesity, elevated blood coagulation, and physical inactivity. Potential risk factors for CAD include high cholesterol, oxidative stress, smoking, high blood pressure, diabetes, age, male sex, high homocysteinemia, inflammatory variables, family history, previous cardiac ischaemia, atherogenic diet, and elevated lipoprotein [9,11–20]. Singlet oxygen, superoxide anion, hydroxyl radical, and hydrogen peroxide (H2O2) are examples of reactive oxygen species (ROS) that are frequently produced during biological reactions or as a result of outside influences. The pathophysiology of degenerative illnesses like atherosclerosis is supported by elevated levels of free radicals and lipid peroxides, which are caused by an excess of ROS that is not eliminated by the antioxidant framework [21–25]. Figure 1 provides a summary of the course of atherosclerosis.

Nuclear factor kappa B (NF-kB) and endotoxin are two of the most well-known signalling pathways that have been linked to the inflammatory response in atherosclerosis. The onset, progression, and development of atherosclerosis—which leads to the formation of atherosclerotic plaque—are influenced by a variety of factors, including immune and inflammatory mediators, genetic and environmental factors, metabolic pathways, receptors, and enzymes. These techniques also help identify novel biomarkers and therapeutic approaches. A brief discussion of the significance of several signalling pathways and possible pharmacological targets in the

management of atherosclerosis is also included in this study. In order to improve CVD prevention, prediction, diagnosis, and prognosis while also being cost-effective, it is essential to identify those who are more likely to experience cardiovascular events (CDEs). Individual risk cannot be accurately predicted by traditional risk indicators, even though they have a high predictive value at the population level. Numerous contemporary vascular biomarkers have also been covered. Circulating plasma biomarkers such as high-density lipoprotein (HDL) and a conceptual change in the assessment of cardiovascular risk away from HDL cholesterol levels and towards HDL function support this. The novel sources of plasma-derived indicators used in today's omics-based research include microparticles, microvesicles, and exosomes. Furthermore, in the hunt for novel biomarkers, such as proteome searches or the detection and measurement of small metabolites like lipids (which are frequently used for metabolomics and lipidomics-level analysis and understanding), mass spectrometry and nuclear magnetic resonance spectroscopy have become important complementary technologies. Pro-inflammatory lipid metabolites have garnered a lot of interest in the cardiovascular field. It is straightforward to improve individual cardiovascular risk identification and diagnosis in the near future by advancing biomarker prediction and identification.

Given the results of recent studies, it is vital to investigate the roles that oxidative stress plays in the formation and progression of artherosclerosis, as shown in Figure 1. Antioxidant agents are substances that have the ability to change the structure and function of biological components and possibly even eradicate reactive oxygen species (ROS) before they contact with them. Flavonoids and other phenolic compounds, which are produced by plants, have several natural functions, including acting as antioxidants in cells. Because they help the body fight oxidative stress by keeping oxidants and antioxidants in balance, plant phytochemicals are good for your health. According to a World Health Organisation (WHO) study, the vast majority of people on the planet use natural treatments for basic medical care. Therapeutic pharmacological efficacy against a range of acute and chronic illnesses has been demonstrated by a number of restorative plant bioactive concentrates and their isolated dynamic constituents. The impact of oxidative stress and its constituents on human well-being has emerged as a significant concern. Reactive oxygen species (ROS) are produced in greater quantities when the body is overworked. Large amounts of ROS are too much for endogenous enzymatic and non-enzymatic antioxidant molecules to handle, which leads to anomalies, cell death, and illnesses. Many people's diets are deficient in antioxidant molecules, which can result in degenerative disorders like cardiovascular disease. Consuming specific plant sources to incorporate antioxidant components into one's everyday diet may help treat related human illnesses. There are associations between the incidence of human disease and the consumption of foods high in antioxidants, and these natural antioxidant sources may be used as a form of preventative medicine. There are fewer synthetic medications available to effectively treat cardiovascular illnesses, especially atherosclerosis, because herbal antioxidants have less side effects than synthetic antioxidants. Antioxidants are abundant in natural goods, and those produced from plants are very helpful in the diagnosis of atherosclerosis.

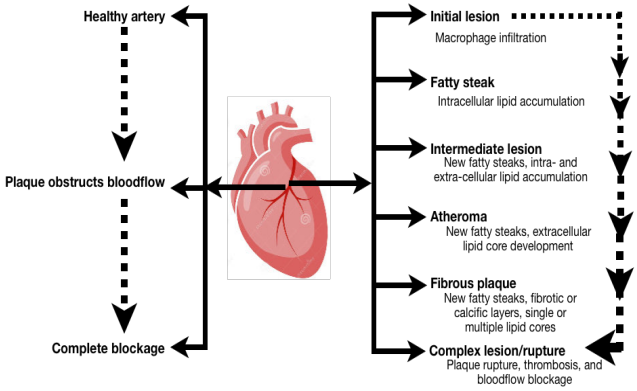

Figure 1. *Atherosclerosis progression. Here, the artherosclerosis progression was shown from initial lesion to complex lesion or rupture.*

The chance of developing clinical symptoms of atherosclerosis can be reduced with early prevention and treatment. Anti-inflammatory, antioxidant, anti-atherogenic, hypotensive, lipid-lowering, and anti-thrombotic properties are the main ways that medicinal plants exhibit their anti-atherosclerotic effects. Additionally, pharmacological compounds derived from medicinal plants are characterised by relative higher safety and fewer side effects, making them one of the more promising and effective anti-atherosclerotic drugs. Additionally, most medicinal herbs have pleiotropic anti-atherosclerotic properties. Previous studies of carotid Intima-media thickness (IMT) progression after long-term medicinal plant therapy have established the direct anti-atherosclerotic activity of several medicinal plants.

By concentrating on atherosclerosis progression from initial lesion to complex lesion or rupture, molecular mechanisms involved in the evolution of the atherosclerotic plaque, including associated pathways and pathway components, and novel targets that act from the beginning stage of plaque formation to thrombus formation in atherosclerosis, this review may help choose the best treatments and prevent plaque complications. Furthermore, promising herbal remedies have been described along with their goals (Figure 2).

2. Pathophysiology and the progression of atherosclerosis

The carotid, coronary, aortic, and iliac arteries are among the arteries that are impacted by the disease atherosclerosis. The pathogenic aetiologies and risk factors for atherosclerosis, a serious treatment concern, include smoking, obesity, diabetes mellitus, hyperlipidaemia, and hypertension [3,11,25-27]. The following illustrates the well-known causes and stages of atherosclerosis (Figure 1). Early phases of atherosclerosis include monocyte attachment to the active endothelium monolayer, migration of linked monocytes into the tunica intima, and maturation of monocytes into macrophages. The absorption of lipid globules by macrophages results in the formation of foam cells. In response to the progression of the lesion, foam cells produce extracellular matrix macromolecules such collagen, elastin, and proteoglycans, multiply resident intimal smooth muscle cells (SMCs), and transfer SMCs from the tunica media to the tunica intima [12,14,28,29]. Muscle cells (MCs) and plaque macrophages may be killed by apoptosis as the lesion progresses. The central part of the plaque may develop a lipid or necrotic core due to extracellular lipid seeping from dead and dying cells. The most visible consequence of atherosclerosis is plaque rupturing or thrombosis, which is the disease's last stage and causes disruptions in blood flow as well as other cardiovascular issues [20,26,30,31].

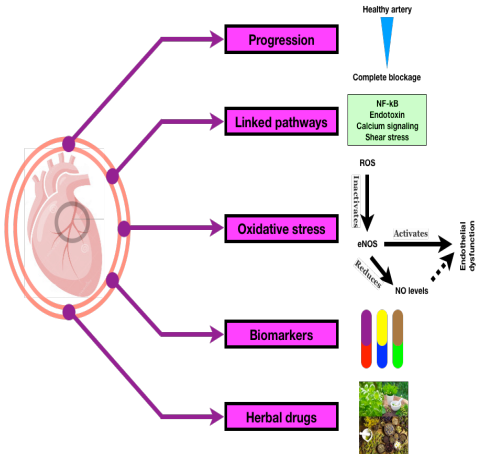

Figure 2. An sketch to display the list of summarized pathways associated with artherosclerosis.

Reduced artery thickness and flexibility are hallmarks of atherosclerosis, a serious cardiovascular disease. An excessive accumulation of plaque around the artery wall results in atherosclerosis, which causes arteries to stiffen and tighten. Basically, plaque blocks blood flow from a healthy artery to a complete blockage. It progresses through several stages: (a) initial lesion (macrophage infiltration), (b) fatty steak (intracellular lipid accumulation), (c) intermediate lesion (new fatty steaks, intra- and extracellular lipid core development), (d) atheroma (new fatty steaks, intra- and extracellular lipid core development), and (e) fibrous plaque (new fatty steaks, fibrotic or calcific layers, single or multiple lipid cores). Finally, plaque ruptures, thrombosis, and blood flow blockage (Figure 1)]. Early phases of atherosclerosis include monocyte attachment to the active endothelium monolayer, migration of linked monocytes into the tunica intima, and maturation of monocytes into macrophages. Major cardiovascular repercussions come from the illness's disruption of blood flow throughout the body [4,10,22,29,35,36]. Arteries include a thin layer of cells called the endothelium, which smoothes the artery and permits blood to flow freely. Endothelial damage is the initial stage of atherosclerosis formation. This leads to the accumulation of low-density lipoprotein (LDL) cholesterol in the artery wall. The inflammatory process starts after this buildup, and macrophages enter the endothelium to remove cholesterol. However, some macrophages get stuck in the damaged area of the artery wall during this process. Plaque, which is composed of macrophage white blood cells and cholesterol, accumulates as a result. The plaque clogs the artery, preventing blood flow. Blood clots may consequently develop, which may result in potentially fatal conditions including heart attacks and other cardiovascular illnesses. The condition known as atherosclerosis harms the arteries all over the body [16,24,37–41]. Atherosclerosis is the primary cause of death in developed countries. Risk factors include things like age, gender, genetic susceptibility, diabetes mellitus, hyperlipidaemia, hypertension, smoking, obesity, and inactivity. Atherosclerosis must be thoroughly investigated since, once it has occurred, it can result in a number of potentially fatal cardiovascular conditions, regardless of the underlying cause or risk factor [4,9,10,26,27,40,42,43].

3. Atherosclerosis-associated pathways and the potential pathway components

The disorder known as atherosclerosis causes serious damage to the arteries, especially the carotid, coronary, aortic, and iliac arteries. This severe therapeutic problem has been exacerbated by pathogenic aetiologies and risk factors, including smoking, obesity, diabetes mellitus, hypertension, hyperlipidaemia, and diabetes [4,9,11,16,19,26,27,37,42,43]. The cause of this type of atherosclerosis is well known, as seen in Figure 1. Better therapy selection and the crucial prevention of plaque complications may result from an understanding of the molecular mechanisms underlying the development of atherosclerotic plaques as well as various novel drug targets that may act from the early stages of plaque formation to thrombus formation. It is now understood to be a chronic inflammatory disease with an autoimmune component, rather than a condition solely brought on by the body's excessive fat buildup, and it is a major cause of death and morbidity [40,44-49]. The distinct genes have been identified and their impact on the development, promotion, and progression of atherosclerosis has been investigated using a range of molecular approaches. Many of these genes and their associated pathways are

unknown to the majority of physicians and researchers. Several key signalling pathways implicated in atherogenesis have already been investigated (Figure 3). Some of the elements and routes that may be connected to the various phases of atherosclerosis progression are as follows: Purinergic signalling, modified lipoprotein activation of endothelial and other cells, ROS effects on signalling, endothelial adaptations to flow, including G protein-coupled receptor (GPCR) and integrin-related signalling, TNF-a and related family members that cause NF-kB activation, and regulation of leukocyte adhesion to endothelial cells Figure 3 provides an overview of the pathways and their constituent parts that may be associated with atherosclerosis [6,10,15,20,23,25,29,32,37,49-53].

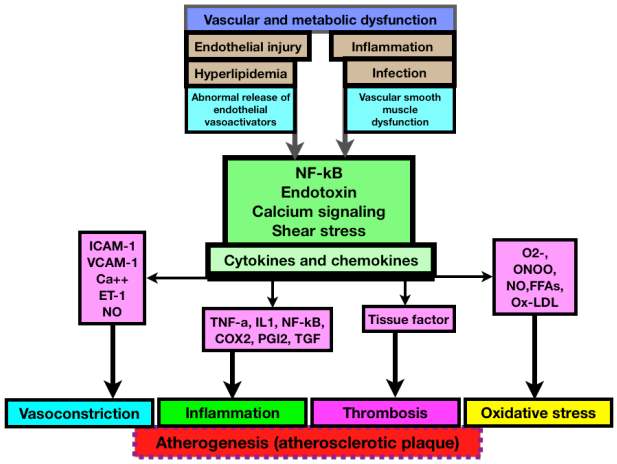

Figure 3. An sketch to display the list of summarized pathways associated with artherosclerosis.

3.1. Immune and inflammation-associated pathways: The development of atherosclerosis is significantly influenced by inflammation, which is constant in stable plaques but active in fragile and burst plaques because the fibrous cap weakens and increases the likelihood of the plaque rupturing. A number of different types of atherosclerotic plaque may be at risk, even if the event can be brought on by the rupture of a single susceptible plaque [5,7,11,32,54]. The several kinds of susceptible plaques show that atherosclerosis is a common inflammatory disease. In order to identify people at higher risk of acute cardiovascular and cerebrovascular events before symptoms manifest, the current objective is to create morphologic and molecular indicators that can distinguish between stable and fragile plaques. With an emphasis on the molecular mechanisms governing plaque formation and serum indicators linked to plaque inflammation, this review examines the natural history of atherosclerotic plaques. It is categorized as a chronic inflammatory disease due to an aberrant interaction between lipids and the immune system [6,11,12,25,48].

Plaque inflammation is caused by a complex interplay of inflammatory mediators in both immunological and non-immune cells. Risk factors cause the circulation and vessel wall to become activated by shear stress, oxidised lipoproteins, and oxidative stress. When risk factors are absent, inflammatory pathways continue to function, leading to persistent, non-resolving inflammation [54–57]. Complex lesions are characterised by significant inflammation, which is associated with the severity of the disease and is prone to rupture and acute events. Therefore, inflammation may contribute to the development of plaque and be a risk factor for atherosclerotic events. A deeper comprehension of the mechanisms behind these inflammatory processes is necessary for better atherosclerotic disease diagnosis and treatment options [29,32,58,59]. Prior research examined potential targets for atherosclerosis treatment as well as the role of significant inflammatory actors and processes in the development of atherosclerotic plaques. Ablation of important inflammatory mediators or cell types has been demonstrated to significantly reduce plaque development, supporting the role of immunological activation in atherosclerosis. Inflammatory diseases, whether communicable or non-communicable, can raise the risk of cardiovascular disease. In both healthy and ill patients, CVD and CRP are separate risk factors for cardiovascular events. From early fatty streaks to late atheromas, immune cells can be found at every stage of the development of atherosclerosis. Lesional inflammation rises as a plaque forms, and it is more noticeable in plaques with sizable necrotic cores. Plaque inflammation is caused by immune cells, smooth muscle cells, platelets, and endothelial cells. Moreover, the complexity of atherosclerotic plaque inflammation is increased by the wide variety of inflammatory stimuli. Every plaque has inflammation [15,53,60]. Additionally, van der Wall et al. found a topographic correlation between thrombosis, plaque rupture, and inflammatory infiltration in patients with fatal AMI, suggesting that macrophages at the site of cap rupture have a pathogenetic role in patients with fatal AMI. Recent studies have shown that activated T cells and active macrophages promote the breakdown of plaque. The production of cytokines and lytic enzymes by a combination of macrophages and lymphocytes weakens the fibrous cap in a susceptible plaque, putting the lesion at danger of rupture[16,19,25,26,61-65].

Nitric oxide (NO) levels are lowered by decreased endothelial biologic activity, which is linked to increased expression of pro-thrombotic factors, pro-inflammatory adhesion molecules, cytokines, and chemotactic proteins [25,29,40,66,67]. Cytokines may decrease NO bioavailability, which raises the production of ROS. ROS lowers NO activity both directly and indirectly by interacting with endothelial cells and oxidising guanylyl cyclase or inducible Nitric Oxide Synthase (iNOS). Vascular adhesion molecule 1 (VCAM-1) is expressed more when NO bioavailability is low. In order to initiate vascular wall invasion, VCAM-1 attaches monocytes and lymphocytes to the

endothelium and raises the production of NF-kB. Another effect of NO is a decrease in leukocyte adhesion. Lowering NO levels increases the synthesis of monocyte chemotactic protein 1 (MCP-1), which attracts monocytes. NO and endothelin 1 work in perfect harmony to regulate vascular tone (ET-1). Patients with advanced atherosclerosis had greater blood levels of ET-1, which is correlated with the severity of the illness. In addition to its vasoconstrictor action, ET-1 promotes leukocyte adhesion and thrombus formation [26,33,68-70]. The defective endothelium expresses P-selectin, which is activated by agonists like thrombin, and E-selectin, which is triggered by interleukin 1 (IL-1) or tumour necrosis factor (TNF). IL-1, TNF, and interferon-IFN are examples of inflammatory cytokines that raise the expression of VCAM-1 by endothelial cells and intercellular adhesion molecule 1 (ICAM-1) by macrophages and endothelium. Endothelial cells produce MCP-1, monocyte colony-stimulating factor (M-CSF), and IL-6, which all contribute to the inflammatory cascade. Smooth muscle cells produce IL-6 to initiate the creation of C-reactive protein (CRP). By aiding in the recruitment of monocytes and encouraging them to create IL-1, IL-6, and TNF, CRP may be a factor in the proinflammatory characteristics of the plaque [5,6,11,30,32,58,71].

Damaged endothelium can allow lipids to enter the sub-endothelial region. Fatty streaks are a feature of the initial stage of atherosclerosis. Many molecular pathways influence the evolution of plaque. When plaque forms, activated endothelial cells increase the expression of inflammatory genes and adhesion molecules [14,23,29,36,37,69,72]. After passing through the bloodstream, monocytes develop into macrophages in the sub-endothelial area. Two macrophage receptors that absorb lipid buildup in the intima are scavenger receptor A (SR-A) and CD36. Lipid-laden macrophages release MMPs, tissue factor, and proinflammatory cytokines, which exacerbate the local inflammatory response in the lesion and result in fatty streaks. In addition to SMC migration and proliferation in the lesion, which results in the formation of a fibrous cap of advanced complicated stable atherosclerotic lesion (i.e., stable plaque), repeated cycles of inflammation cause a concentration of macrophages, some of which may die in this area, creating a necrotic core. Heat shock proteins (HSP) and OxLDL are examples of endogenous or microbial antigens (Ag) that T lymphocytes may encounter. Numerous effector pathways can be triggered by immune responses. The expression of fractalkine (CX3CL1) increases when IFN- and TNF- are combined. This cytokine network facilitates the Th1 pathway, a highly proinflammatory system that triggers the formation of superoxide, protease activity, and macrophage activation. A strong inflammatory cascade that is triggered by the recruitment and activation of Th1 T cells favours the conversion of a stable plaque into an unstable or burst plaque [4,15,19,20,31,47,70,73-75].

3.2. *Receptor tyrosine kinases*: A surprisingly wide range of signalling mechanisms, including modifications to membrane lipid components and signalling protein translocation to cell membranes, take place close to cell membranes. The actions of insulin receptor (INSR) signalling and receptor tyrosine kinases (RTK) lend credence to this notion [4,76-79]. Increased atherosclerosis (IGF-IR) was caused by reduction of insulin secretion, endothelial-specific INSR KO, and knockout of the very similar insulin-like growth factor I receptor in other cells. The relevance of these signalling networks is further enhanced by the diverse impacts on atherosclerosis brought about by genetic alterations in downstream components. RTK is activated by a number of growth hormones, including insulin, IGF-I, PDGF, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and many others [20,23,29,80,81]. Many cells in culture experience spontaneous apoptosis when these triggers are not present. It is easy to assume that one of the anti-atherogenic consequences of INSR and IGF-IR signalling is the suppression of apoptosis. It is anticipated that additional insulin signalling components will also play a part. For instance, it has been shown that insulin increases the function of the endothelial cell-cell barrier at adherens junctions, indicating that it may have anti-inflammatory effects [3,6,25,53,66,82-84].

Adapters are attracted to phosphotyrosines on the cytoplasmic tail of the receptor when INSR tyrosine self-phosphorylation takes place. Once connected, the active tyrosine kinase domain of the receptor may tyrosine phosphorylate these adaptors. IRS proteins (isoforms IRS1–4) serve as evidence for this. On the other hand, insulin resistance and feedback inhibition might be caused by downstream signalling, which can be blocked by serine phosphorylation of IRS [6,52,60,66,85,86].

In addition to signalling enzymes like Src (presumably via IRS for INSR), SH2 domain-containing tyrosine phosphatase (SHP2), and Src homology collagen-like (Shc), other adapters that bind tyrosine phosphorylated INSR (and other RTK) include growth factor receptor-bound protein 2 (Grb2), Grb2-associated binder 1 (Gab1), and Src homology collagen-like. Gab1 binds phosphotyrosine on active INSR, like IRS proteins do, gets phosphorylated on tyrosine by INSR, and then binds PI3K to further increase PIP3 synthesis. The cytoplasmic tail of RTK and other non-tyrosine kinase receptors or adapters (like Shc) can be phosphorylated by the Src family of non-receptor tyrosine kinases. Consequently, Src family kinases either increase RTK activity, including mitogenic activity, or initiate downstream signalling [50,78,87,88]. The tyrosine kinase Janus kinase (JAK) is brought to INSR by the adaptor SH2b adapter protein 1 (SH2B1), while the adapter receptor for activated C-kinase 1 (RACK1) seems to carry a JAK substrate, signal transducer and activator of transcription 3 (STAT3). JAK tyrosine kinases phosphorylate signal transducer and activator of transcription (STAT) proteins, which then dimerise and move to

the nucleus to act as transcription factors. The JAK-STAT system is among the fastest and most efficient receptor-activated pathways. JAK-STAT transducers are present in a number of receptors, including interleukin receptors [15,29,89-92].

The fact that different INSR-activated pathways are advantageous to one another should not be overlooked. Superoxide and hydrogen peroxide are commonly produced by the activation of NOX isoforms and calcium-sensitive dual oxidase (DUOX) enzymes by RTK and numerous other receptors. These ROS inhibit the lipid phosphatase PTEN and other protein tyrosine phosphatases (PTP) in a reversible fashion. The 3 phosphate from PIP3 is broken down by PTEN. Tyrosine phosphatases, including PTEN, can become so active that they are unable to transmit any signals until they are deactivated [15,31,91]. In order to extend their signals, the majority of cellular activation systems—whether pro- or anti-inflammatory—increase the production of ROS simultaneously. These systems include thrombin, ANG II, antigen recognition, cytokines, growth factors, and even insulin. Consequently, ROS have a significant signalling function in preventing the transmission of RTK (and other) signals. Endothelial cell membranes produce far less superoxide than fully active NOX2 in neutrophils and other phagocytes, despite carrying the same NOX2 and other NOX isoforms [23,80].

3.3. MAPK signaling pathway: One of the main pathways that RTK ligation triggers is MAPK signalling, which has been thoroughly investigated and analysed from a variety of angles and methods and has been connected to a number of important biological processes as well as human illnesses. Receiving input signals from multiple receptors, G protein switches, ROS, integrins, and other cellular sensors, MAPK modules act as signalling bottlenecks. They then transduce these signals into a tightly controlled on-off signal that is sent to a range of cellular effectors and in various types of controlling systems, such as feedback and feedforward (both positive and negative) controls. Additionally, they may transduce signals to other pathways through pathway crosstalk [93–106]. As a result of its ability to phosphorylate over 100 proteins, ERK1/2 and the proteins it phosphorylates are known to mediate metabolism, gene transcription, cell architecture, differentiation, cell survival, proliferation, and death. Atherosclerosis progression is associated with some of these vital biological processes [32,49,50,53,104,107-113].

One of the potential targets of ERK1/2 is MSK1, a mitogen- and stress-activated protein kinase that translocates to the nucleus and phosphorylates S276 of the NF-kB p65 subunit. MSK1 phosphorylates S276 of the NF-kB p65 subunit after translocating to the nucleus during activation [114,115]. This significant p65 modification increases MAPK and allows NF-kB to have complete transcriptional competence: Crosstalk in NF-kB signalling [116–119]. JNK triggers the activation of activator protein-1 (AP-1), activating transcription factor-2 (ATF2), and early growth response factor-1 (EGR1), which includes c-FOS, c-JUN, or both. It is well known that both AP-1 and EGR1 stimulate the transcription of proinflammatory genes. In ApoE-deficient animal models, EGR1 deletion has been demonstrated to reduce atherosclerosis [8,18,21,50,54,66,87,120,121].

In regions of disrupted flow, MAPK p38 activation seems to be a crucial step in getting endothelial cells ready for ATF2 and AP-1 activation. MAPK-activated kinase 2 (MK2) phosphorylates p47phox, a 390 amino acid protein with multiple functional domains, including a proline rich domain (PRR), two src homology 3 (SH3) domains, an auto-inhibitory region (AIR), and one phox homology (PX) domain, in order to increase NOX activation and ROS generation [18,44,49,71,120,122]. The presence of AU-rich sequences in the 3' untranslated regions of several proinflammatory proteins with high turnover rates suggests that MK2 contributes to mRNA stabilisation for these proteins. While p38 knockdown has no effect on atherosclerosis, MK2 knockout decreases atherosclerosis while increasing susceptibility to infection [7,11,15,19,33,84,107,122-124]. In endothelial insulin signalling, the antiapoptotic, anti-inflammatory, and vasodilatory PKB-eNOS pathway, the potential pro-inflammatory Grb2-Sos-Ras-Raf1-MAPK cascade, and the production of the vasoconstrictor endothelin-1 (ET-1) function as two opposing forces. The hypothesis was corroborated by the observation that in ApoE-deficient animals with IRS2 deletion, elevated atherosclerosis was proportionate to plasma insulin concentrations. In general, normal insulin signalling protects the endothelium [52,59,60].

Finally, based on earlier research, we have compiled a summary of the signalling pathways and roles linked to artherosclerosis here. In summary, mainly inflammation associated pathways (such as cytokine and chemokine signalling, NF-kB signalling, COX2, PGI2, and TGF), calcium signalling, shear stress, MAPK, PI3K-AKT, JAK-STAT, matrix metalloproteinases (MMPs), Notch signalling, Wnt, Shh, VEGF, FGF, IGF 1, HGF, EGF, FOXO, CREB, PTEN, EGFR, BCL-2, NGF, BDNF, neurotrophins, growth factors, several apoptotic pathways, ET-1, NF-κB, TNF alpha, angiopoietin, and there are a number of signalling proteins IFN, TFs, NOs, serum cholesterol, LDL, ephrin, its receptor pathway, HoxA5, KLF3, KLF4, BMPs, TGFs and more.

4. Role of oxidative stress and ROS in progression of Atherosclerosis

Oxidative stress, which is defined by an increase in the production of free oxygen radicals and is one of the basic pathogenetic processes of atherosclerosis, is closely linked to endothelial dysfunction, a common

condition that predisposes to atherosclerosis and stimulates the vascular inflammatory response. Numerous atherosclerosis risk factors, including smoking, hypertension, diabetes, and high cholesterol, have been shown to be associated with oxidative stress in prior studies [4,9,10,16,17,20,26,40,42,43,61,70,125].

It is now generally accepted that H2O2 facilitates or modulates inflammatory signalling instead of directly inducing NF-kB activation as was once believed. Additionally, it has effects that are particular to certain cells and contexts; arterial endothelial cells, for example, are more resilient to adverse effects than many other cell types. Vasodilation is induced by H2O2, a crucial endothelial-derived hyperpolarising factor (EDHF), which activates a potassium channel in vascular smooth muscle cells (VSMCs). However, ROS might also increase the activation of other pathways that interact with NF-kB, like the ASK1-JNK pathway (Figure 3). Reactive nitrogen species (RNS) include NO and peroxynitrite, which are produced when NO and superoxide quickly combine. RNS can have effects that are similar to or completely different from those of ROS through its interactions with signalling proteins [22,23,44,47,126]. According to recent studies, distinct, distinct, reversible posttranslational modifications involving specific cysteine sulfhydryl groups are responsible for ROS- and RNS-mediated signal transduction. Spontaneous or catalysed conversions from reduced to oxidised cysteine change the activity, binding, and signalling characteristics of many redox-sensitive proteins, typically in a context-appropriate and harmonic way. In fact, because ROS-mediated signalling involves many proteins in normal physiology, it is beginning to resemble phosphorylative signalling. This should include the effects of hydrogen sulphide (H2S), which targets cysteine sulfhydryl groups in a similar manner. Therefore, ROS-induced protein modification and redox-sensitive signalling can be viewed as essential adaptations that enable cells to benefit from an environment that always contains ROS. The widespread notion that ROS and RNS are evils that must be eradicated at all costs stands in stark contrast to this. Indeed, activation, cell survival, proliferation, stress adaptation, cell motility, vasodilation, and angiogenesis are only a few of the critical signalling pathways that depend on a little quantity of controlled ROS. Increasing ROS levels cause necrosis and apoptosis, although in many situations, such as when phagocytes generate ROS to destroy cancerous, virally contaminated, or otherwise irreversibly damaged cells, these responses can be seen as normal and adaptive. A delicate balance between the anti- and proapoptotic actions of ROS is implied by the numerous instances of cancer-promoting mutations or knockouts that are resistant to ROS-induced apoptosis. One early result of ROS was the inactivation of a number of enzymes that have a vulnerable, catalytically necessary cysteine in their active site [15,26,59-61,86,127].

The defensive mechanisms of endogenous antioxidant agents and the generation of reactive oxygen species, or free radicals, are always in balance in a normal and healthy organism. Oxidative stress and other problems could arise if this equilibrium is upset. In addition to causing cell death, this oxidative stress state has the capacity to destroy all vital cell constituents, such as proteins, DNA, and layer lipids. Because of this, it can lead to a variety of illnesses, including cardiovascular issues like atherosclerosis. Endothelial cells experience oxidative stress due to three factors: (1) xanthine oxidase, (2) nicotine-amide adenine dinucleotide phosphate (NADPH) oxidases, and (3) a disruption of the mitochondrial electron transport chain structure. Numerous investigations have demonstrated that NADPH oxidase(s) contribute to the vascular formation of ROS, even though only a small portion of the enzyme has been discovered in the vascular tissue of a few animal species, including humans [4,15,17,40,128,129]. Oxidative stress in endothelial cells is caused by three factors: xanthine oxidase, nicotine-amide adenine dinucleotide phosphate (NADPH) oxidases, and mitochondrial electron transport chain framework dysfunction. Numerous investigations have shown that NADPH oxidase(s) contribute to the vascular formation of ROS, even though only a small portion of NADPH oxidase has been found in the vascular tissue of a few animal species, including humans.

It is mostly conveyed by the endothelium, and its level is increased in a NADPH oxidase-dependent manner by angiotensin II or oscillatory shear stress. By generating reactive oxygen species (ROS) when oxidative stress is present, xanthinoxidase has been connected in numerous studies to the development of atherosclerosis [4,6,20,23,26,69,70,130]. Mitochondria are among the most significant intracellular ROS producers. During oxidative phosphorylation, O-is produced as a byproduct of electron transport via the mitochondrial electron transport chain. The majority of O- is normally produced inside the mitochondrial structure and rummaged by glutathione peroxidase and Mn-SOD. When O-production is high, anion channels allow H2O2 and O- to escape to the space between the film and the cytosol. Damage to the mitochondria's coupling state leads to electron spill and increased production of ROS. During mitochondrial uncoupling, a large number of protons return to the mitochondrial grid, avoiding the ATP synthase pathway and generating ROS. A decrease in electron transport chain activity in the respiratory complex caused by a paraoxonase 2 (PON2) deficit was connected to the buildup of ROS and the advancement of atherosclerosis [23].

Endothelial cells experience oxidative stress due to three factors: At different stages, expanded ROS contribute to the development of atherosclerosis. One important early stage in the development of atherosclerosis is endothelial dysfunction. Endothelial nitric oxide synthase (eNOS) inactivation and a drop in nitric oxide (NO)

levels have been recognised as causes of endothelial dysfunction. Under typical circumstances, eNOS converts L-arginine to L-citrulline, which generates NO. The substrate L-arginine and basic cofactors like tetrahydrobiopterin (BH4) are necessary for eNOS to function. The process known as "uncoupling" occurs when eNOS produces O rather than NO when L-arginine or BH4 levels are low. One of the main causes of vascular endothelial dysfunction is the extremely rapid interaction of O- with NO- to make peroxynitrite (ONOO), even though the production of ONOO reduces NO- bioavailability and creates an even more harmful radical (ONOO). Additionally, ROS triggers the assembly of adhesion molecules such as ICAM-1 and VCAM-1, which may encourage the attachment of inflammatory cells and the deposition of lipids in the intimal layer. During the phase of inflammatory cell activation, VCAM-1 promotes monocyte integration into the sub-endothelial region. Cytokines cause monocytes to develop into macrophages. LDL quickly peroxides to ox-LDL as the lipid deposition process progresses, and forager receptors on freshly activated macrophages in the artery linings detect this protein. When ox-LDL is phagocytosed by macrophages, the lipoprotein gets stuck in the intima, which makes the macrophages grow and create foam cells. Reactive oxygen species' (ROS) pathophysiological role in the onset and progression of atherosclerosis in several systems, as well as the various locations where antioxidant compounds found in herbal products may be able to slow or even reverse the progression of atherosclerosis [34,40,51,60,61,70,72,131].

The main risk factors for artherosclerosis are smoking, high blood pressure, high cholesterol, and diabetes. Increased oxidative stress and the resulting generation of superoxide anion in vascular cells promote the conversion of LDL to more atherogenic oxidised LDL (ox-LDL). Ox-LDL has also been discovered to be a potent inducer of vascular oxygen radical generation, increasing oxidative stress and causing the inflammatory disease known as atherosclerosis. Oxidatively altered LDL is one of the most studied alterations and has been recognised as an indicator of oxidative stress. Given that atherosclerosis is essentially an inflammatory disease, atherogenic stimuli like high blood pressure have a tendency to trigger the inflammatory response through oxidative stress by causing the development of recruiting pathways for mononuclear leukocytes. Vascular cell adhesion molecule-1, one of these genes, is affected by transcriptional factors that are impacted by oxidative stress, which modifies the redox state of endothelial cells [4,26,27,43]. Additionally, oxidative stress on the arterial wall brought on by high blood pressure has been shown to promote and hasten atherosclerosis. Nitric oxide availability for smooth muscle relaxation can be decreased by elevated superoxide levels caused by increased production of oxidants such superoxide anion. Superoxide and hydrogen peroxide increase the synthesis of endothelin-1, which causes vasoconstriction and high blood pressure. Diabetes: People with diabetes have increased LDL peroxidation. Increased cholesterol autooxidation was also observed in patients with type 2 diabetes who had normal cholesterol levels. Smoking: There are several reactive oxidants, such as hydrogen peroxide and free radicals (H2O2), in cigarette smoke. According to numerous research, smoking is a frequent way to induce inflammation and oxidative stress. Agarwal's research indicates that smokers' plasma and urine have increased amounts of oxidative stress indicators, such as malondialdehyde (MDA) [20,26,27,29,43,121].

5. Potential atherosclerosis biomarkers

Instead of being a condition brought on exclusively by the body's high lipid levels, it is now understood to be a chronic inflammatory disease with an autoimmune component. Studies that look at the relationships between molecular and cellular components typically concentrate on the pathophysiologic elements of atherosclerosis. To further expand the pathogenetic processes, the emphasis has now shifted to new risk factors and genetic predisposition. Since inflammation is currently the most accurate cause of atherosclerosis, it is imperative that we learn more about these processes in order to develop new indicators and treatments that target particular pathways. Additionally, the knowledge and advancement of chronic diseases like atherosclerosis are guided by the diagnosis and treatment of these conditions [4,44,66,70,132,133]. Therefore, more precise illness detection and treatment will be made possible by improved targeting and comprehension of biochemical pathways. Moreover, antihyperlipidemic and anti-inflammatory drugs were only a possibility and had only mediocre effects when used to treat atherosclerosis. The endoglin receptor, PPAR, squalene synthase, thyroid hormone analogues, scavenger receptors, leucotriene receptors, calcium signalling, pentraxin, nitric oxide, heat shock proteins, liver X receptors, shear stress pathway, CD14, endotoxin signalling, and nuclear factor kappa B are some of the more recent areas or novel drug targets that will allow for improved. Consequently, we looked into the molecular processes that underlie the development of atherosclerotic plaques as well as a number of new targets that might function from the earliest phases of plaque formation to the formation of thrombus in atherosclerosis, which could lead to improved treatment strategies and the avoidance of plaque complications [11,17,25,127,134].

We have examined the wide range of biomolecules that serve as biomarkers for artherosclerosis, such as transcriptomic, genetic, epigenetic, proteomic, and metabolomic biomarkers at different stages of the disease's progression. We have also possibly investigated biomarkers and their primary applications in diagnosis, prognosis, and treatment decision-making. Biomarkers might be genetic, transcriptomic, epigenetic, proteomic, or

metabolomic, and they are frequently categorised into three groups: predictive, prognostic, and diagnostic. Both in clinical practice, where they are utilised for risk assessment, diagnosis, prognosis, therapy efficacy, and relapse determination, and in the search and development of new medications, these biomarkers are essential. Biomarkers for atherosclerosis are increasingly being used in cancer molecular diagnostics. To decide whether and in what context a biomarker is helpful for patient care, as well as whether additional testing is necessary before it can be incorporated into standard medical practice, clinicians and researchers need to have a solid understanding of the molecular aspects, clinical utility, and reliability of biomarkers. By linking medicines and diagnostics, biomarkers have the potential to promote personalised treatment [5,27,37,43,64,73,135,136].

An acute phase protein and biochemical indicator with strong predictive power for cardiovascular events is C-reactive protein (CRP). The pathogenesis of atherosclerosis has been connected to the interleukins IL-1 and IL-6, which are also associated to CRP. The apolipoproteins ApoA-I and ApoB are the main lipid metabolic markers linked to the onset and advancement of atherosclerosis. Another important independent risk factor for cardiovascular events is fibrinogen. Finding the associated biomarkers is essential since premature atherosclerosis develops prior to the onset of CVD. To find out if these signs may be utilised to predict future cardiovascular events, more research is necessary. An important factor in the development of atherosclerosis is the existence of inflammation. The procedure also activates the nuclear factor-kappa B (NF-kB) and protein kinase C (PKC) pathways. This results in the upregulation of adhesion molecules on the surface of endothelial cells, the activation of the angiotensin converting enzyme, and the local creation of angiotensin II. These developments may lead to endothelial dysfunction. The most widely utilised inflammatory markers to evaluate early atherosclerosis are CRP and IL-1, IL-6, and IL-18 [11,29,47,64,75].

5.1 Metabolic Markers: The collection of all the metabolites in a biological specimen is called the metabolome. It is a very complex mixture of metabolites from different chemical classes (such as lipids, amino acids, steroids, nucleosides, and so forth), with varying chemical properties (such as hydrophilic versus hydrophilic), and a dynamic range of molecular concentrations. The chemical complexity of metabolomics is increased by the fact that metabolites can undergo a number of chemical modifications, such as oxidation, glycosylation, and methylation. Therefore, metabolomics-based research requires advanced biochemoinformatic techniques and state-of-the-art analytical instruments. A variety of analytical platforms have been developed for metabolomic studies. The most widely used techniques in metabolomics research are gas chromatography (GC) combined with mass spectrometry (MS) or nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography (LC). However, the entire metabolome cannot yet be detected by a single analytical instrument. As a result, the choice of platform is impacted not only by the study's breadth but also by the type of material and methods that are available. In the best case, several platforms that can each identify different kinds of metabolites can be used in tandem with one another. Advances in technology have made it possible to characterise thousands of metabolites, which has led to the development of focused and untargeted, or comprehensive, metabolomics. Targeted metabolomics is the study of a particular group of identified metabolites, typically concentrating on one or more metabolic pathways of interest. This approach is commonly employed in hypothesis-driven research to address certain biochemical problems, such figuring out how a medication affects a specific route. Whereas targeted metabolomics is hypothesis driven and necessitates functional analysis of identified metabolites, elucidation of new pathways, and hypothesis validation, untargeted metabolomics generates hypotheses. Two of the most prevalent metabolic markers of insulin resistance are insulin and glucose. Recent studies have concentrated on inflammatory cytokines released by adipose tissue (like TNF) or in reaction to their release (like CRP), as well as adipokines like resistin and leptin that may play a part in atherogenesis. Adipose tissue produces the vasoprotective cytokine adiponectin, which may be a predictor of a favourable cardiovascular outcome [3,19,26,27,51,53,86,137,138].

5.2 Lipid Markers: Apolipoprotein (Apo B) and low-density lipoprotein (LDL) are still the main targets for treating atherosclerosis and are used to measure plasma atherogeneity. Recent studies have focused on the Apo B: Apo A-1 ratio. At the American Diabetic Association's consensus meeting, it was emphasised how useful the Apo B level is as a predictor of perioperative cardiovascular events (CVE) in patients taking statin medication. As per the guidelines, individuals with diabetes or cardiovascular disease (CVD) risk factors should aim for 90 mg/dL of Apo B, whereas those with diabetes or CVD who also have another CVD risk factor should aim for 80 mg/dL. In addition to the conventional LDL and high-density lipoprotein (HDL) cholesterol (Lp-PLA2), other lipid indicators include lipoprotein (a) [Lp(a)], small dense LDL cholesterol, OxLDL cholesterol, and lipoprotein-associated phospholipase A2 [16,27,35,43,55,70]. One of the main causes of the formation of foam cells is the oxidation of cholesterol, which mostly takes place in the diseased vascular wall. The type of oxidised lipid or apolipoprotein determines the different forms of oxLDL cholesterol. Human carotid and coronary arteries contain large amounts of OxLDL, and more importantly, unstable plaques seem to be specifically concentrated in OxLDL. The involvement of OxLDL in preclinical atherosclerosis, endothelial dysfunction, stable CAD, ACS, percutaneous coronary intervention, and

statin response has been the subject of an increasing number of studies in recent years. In asymptomatic patients, elevated OxLDL cholesterol levels are associated with reduced flow-mediated vasodilation and increased carotid artery intima–media thickness. Blood levels of OxLDL are associated with the presence of CAD. Toshima et al. discovered that the area under the curve for OxLDL-DLH3 levels on receiver operating characteristic curves was larger than that for total cholesterol, apolipoprotein B, HDL-C, and triglyceride levels, and that plasma OxLDL-DLH3 levels were higher in CAD patients than in healthy control subjects [12,13,52,60,64,71,75,135].

5.3 Markers of Plaque Neovascularization and Thrombosis: Numerous clinical and experimental investigations have linked plaque neovascularisation to the development and progression of plaque. Two angiogenic cytokines that may serve as indicators for these processes are placental growth factor and stroma-derived factor 1. Nicotine is an angiogenic agent that accelerates the development of plaque. Nicotine worsened neovascularisation and plaque formation in a model of hypercholesterolemic, apolipoprotein E-deficient mice. The primary cause of thrombosis after plaque rupture is tissue factor, a thrombogenic protein secreted by macrophages. Patients with many cardiovascular risk factors had greater blood levels of tissue factor, which is highly concentrated in the lipid core [16,29,50,64,69,135].

5.4 Markers of Endothelial Dysfunction: It is believed that endothelial dysfunction plays a significant role in the initiation of ACS as well as the development and progression of atherosclerosis. Leukocytes are believed to be directly responsible for endothelium damage in this case. Regardless of the underlying cause, endothelial dysfunction and damage are essential for atherogenesis and the onset of ACS. Numerous studies have demonstrated that endothelial vasodilator dysfunction is an independent predictor of cardiovascular events. The endothelium releases prostacyclin, NO, and other vasodilators in response to acetylcholine. Studies of acetylcholine-induced vasoreactivity in catheterisation patients showed vasoconstriction rather than vasodilation in response to acetylcholine in individuals with endothelial vasodilator malfunction. The prognosis was worse for patients who responded abnormally than for those who responded consistently. Potential indicators of endothelial dysfunction include von Willebrand factor, soluble vascular adhesion molecules, NO, asymmetric dimethylarginine (ADMA), and endothelial progenitor cells. NO is a vasoprotector and vasodilator that prevents platelet adherence and aggregation, leukocyte adhesion, and muscle cell proliferation. In the circulatory system, ADMA, an arginine analogue, competes with arginine and reduces the production of NO. Numerous studies have shown that ADMA may predispose people to cardiovascular events and that its levels are higher in those with cardiovascular risk factors. Von Willebrand factor and soluble vascular adhesion molecules are known to increase in endothelial dysfunction [16,26,31,52,60,64,69,70,75,82]. Endothelial progenitor cells are bone marrow-derived endothelium and vascular smooth muscle cell stem cells that can help with angiogenesis or resurface damaged endothelium. Recent studies have shown a direct correlation between progenitor cell count and the endothelium vasodilator response and a negative correlation with ADMA and serious cardiovascular events. Since it is challenging to evaluate endothelial progenitor cells directly, sKit ligand and stroma-derived factor—both of which are abundant and aid in mobilising endothelial progenitor cells from the bone marrow—are considered putative biomarkers of circulating endothelial progenitor cells [4,31,60,139-141].

5.5 Oxidative Stress Markers: Oxidative stress has a critical role in atherogenesis. There is evidence that vascular oxidative enzyme activation results in lipid oxidation, foam cell formation, vascular adhesion molecule and chemokine expression, and ultimately atherogenesis. A heme peroxidase called myeloperoxidase (MPO) is secreted in inflammatory regions and is present in activated phagocytes. Through the production of several reactive, oxidation-derived intermediates, all of which are mediated by an interaction with hydrogen peroxide, MPO can result in oxidative damage to cells and tissues. Through nitrated apolipoprotein B-100 on LDL and absorption by scavenger receptors, MPO oxidation products are found in significantly greater amounts on LDL isolated from atherosclerotic lesions (up to 100 times higher than circulating LDL) and aid in the rapid generation of foam cells [25,34,53,69,70]. Growing evidence suggests that MPO may contribute to plaque vulnerability. Sugiyama et al. found that MPO was formed at the sites of plaque rupture, in superficial erosions, and in the lipid core, but not in fatty streaks, in advanced ruptured human atherosclerotic plaques derived from individuals who had sudden cardiac death. Furthermore, in the culprit lesions of these individuals, MPO macrophage expression and HOCl immunochemically colocalized. In vitro, MPO-positive macrophages produce MPO and HOCl in response to a variety of inflammatory stimuli, such as cholesterol crystals and CD40L. Genetic variations that result in MPO deficiency or decreased activity are linked to lower cardiovascular risk, which is consistent with MPO's likely participation in the atherosclerotic process, though it is unknown whether these findings are generalisable. In addition to the effects of MPO on NO, MPO-induced LDL oxidation, and the presence of MPO within ruptured plaques, a number of recent clinical studies have demonstrated that MPO levels may provide diagnostic and prognostic information regarding endothelial function, angiographically determined CAD, and ACS [5,23,25,64,131,142-144]. According to the current findings, MPO may be used as a disease marker, offering independent information on diagnosis and prognosis for people experiencing chest pain. It may also be used as

a potential marker for evaluating plaque instability and progression during acute ischaemia [17,19,24,61,63,130,135,145,146].

5.6 MicroRNAs as Potential Biomarkers in Atherosclerosis: It has been demonstrated that microRNAs (miRNAs), a class of non-coding single-stranded RNA molecules, control post-transcriptional gene expression and, consequently, coordinate the expression of cellular proteins. They therefore play a part in the cellular and molecular mechanisms of human illnesses like atherosclerosis in addition to cell-specific physiological functions. MiRNAs may play a part in the creation and progression of atherosclerotic plaques by influencing endothelial integrity, vascular smooth muscle and inflammatory cell activity, and cellular cholesterol homeostasis. Additionally, the expression patterns of many miRNAs differ between patients with atherosclerosis and those with cardiovascular disease. This study looked at the data supporting the many important roles of miRNAs and the molecular processes that underlie them in the onset and advancement of atherosclerosis. Additionally, miRNAs' effects on atherosclerosis have made it possible to exploit them as novel therapeutic targets and diagnostic biomarkers, which could lead to better management of both atherosclerosis and CVDs [5,7,31,43,49,52,73,77,124,147,148].

6. Medicinal Plants and its Products Used as Potential drugs for Targeting Anti-Atherosclerotic Mechanisms and Efficacy

The pathophysiology of atherosclerosis is still being studied by a wide range of experts worldwide, despite significant advancements in recent decades in our understanding of the mechanics of atherosclerotic lesion growth. However, key aspects of the pathophysiology of atherosclerosis are known, and potential pathogenetic pathways of medicinal plants' anti-atherosclerotic effects are being investigated in human, animal, and cell cultures [12,19,21,22,25,136,149]. Several studies have connected the development of atherosclerotic lesions in the artery wall to pro-inflammatory cytokines. Anti-cytokine therapy might be a viable choice for treating abnormalities in the early phases of atherosclerosis formation, according to the findings of these research. Components of a variety of medicinal plants have been found to have the ability to modify inflammatory response pathways, according to recent research [44,49,79,122,127,138,150-153]. Figure 4 summarised the aims of herbal drugs at various stages.

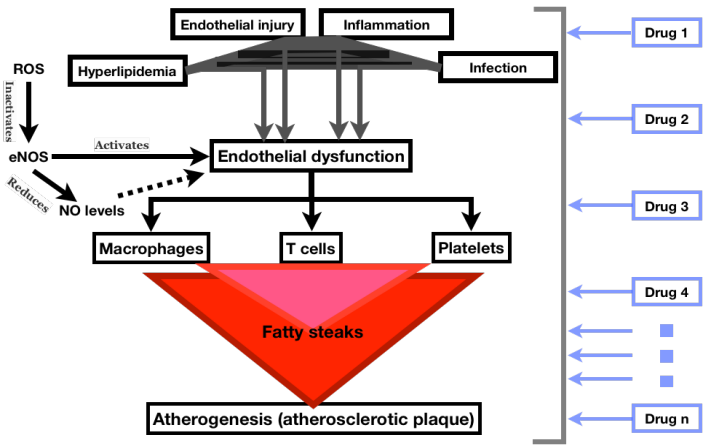

Figure 4. Docking score and H-bond interaction of compounds with E-selectin and L-Selectin.

Since most of these natural substances have little side effects and many of them function as anti-cytokines, they can be used to treat and prevent atherosclerosis over the long term. Through an unidentified mechanism, the herbal preparation Inflaminat, which contains a combination of calendula (Calendula officinalis L.), violet tricolour (Viola tricolour L.), and black elder (Sambucus nigra L.), significantly reduces serum atherogenic activities in an ex vivo model and inhibits the expression of inflammatory cytokines by inhibiting IL-6 and TNF-expression. According to Glycyrrhiza glabra L., liquorice contains a flavonoid called Glabridin, which has been shown to have a number of anti-inflammatory and anti-atherosclerotic properties. Glabridin possesses anti-inflammatory properties and inhibits JNK and NF-kB, which reduces TNF-stimulated gene synthesis of VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1). Glabridin has anti-cytokine activity by inhibiting the synthesis of adhesion molecules in human umbilical vein endothelial cells and the generation of inflammatory cytokines TNF- and IL-1 in microglial cells when activated by LPS [44,79,113,127,138,150,151]. Along with its anti-inflammatory qualities (AAPH), Glabridin may also inhibit LDL oxidation by inhibiting 2,2-azobis(2-amidinopropane) hydrochloride, which stimulated the production of cholesteryl linoleate hydroperoxide in LDL. In an ex vivo model, Glabridin decreased LDL oxidation: mouse peritoneal macrophage cell culture showed a decrease in its ability to oxidise LDL. Plants and plant mixes are extensively used in traditional Chinese medicine to treat atherosclerosis and other cardiovascular issues.

7. Computational approach and its roles in understanding artherosclerosis and diagnostics approach and the solutions

The investigation of complicated and multifaceted interactions in human diseases has been transformed by the omics revolution. Large volumes of biological data can now be produced more quickly and easily thanks to the rapid improvements in omics analysis speed and scale over the past few decades. Finding relevant information in

this "sea of data" is still quite challenging, though [154–162]. One area of biology that approaches the integration of multilayer biological data holistically is called integrative biology. This chapter introduces the concepts and methods for integrating multilayer omics datasets and evaluating single-layer omics data to derive significant and pertinent biological insights. Researching a range of human illnesses may be possible with integrative biology. We also go over some of the current problems in the discipline, like the need for more specialised and interpretable methods and strategies to increase integrative analysis's accessibility for the scientific community. Selecting which genes to look at can be challenging, even though candidate gene association studies are still the most practical and popular approach in disease gene research for complex disorders. To find and rank disease candidate genes, several computer techniques are available [163–169].

Our capacity to comprehend the implications of new knowledge for the prevention, diagnosis, and treatment of common complex human diseases has greatly surpassed our capacity to produce it in the fields of genomics and genetics. For geneticists and computational biologists, the abundance of genetic data has presented a number of important computational and statistical challenges. The first of these challenges is the variable selection problem. This problem stems from the growing understanding that the risk of common multifactorial diseases is more likely to be predicted by the interplay of multiple genetic and environmental factors than by any one component alone. In our genetic study, we should look at combinations of genetic variations or gene expression factors rather than one variable at a time, because interactions are crucial in the aetiology of disease. The issue is that there are practically an infinite number of possible combinations that can be evaluated when there are a lot of variables [170-176]. The second challenge is the feature selection or statistical modelling problem. In other words, what is the most effective technique to model the relationship between clinical outcomes and genetic variations or gene expression variables? Logistic regression is a parametric statistical technique used to relate one or more independent or explanatory factors to a dependent or outcome variable (such as illness status) that has a binomial distribution. However, the number of potential interaction terms increases quickly as more main factors are included in the logistic regression model. Consequently, the ability of logistic regression to handle interaction data is constrained. Although they are versatile, nonparametric, and do not require a genetic model, other techniques like multifactor dimensionality reduction, cellular automata, and symbolic discriminant analysis compromise computational efficiency. Similar to the variable selection problem, there exists an almost infinite number of different model forms [177–181].

Networks of interrelated biomolecules have a major role in controlling the behaviour of cells. Biological components serve as nodes, and interactions between two components serve as "edges." Almost all biological processes may be characterised as interaction networks. Important insights into control mechanisms can be obtained by looking at the basic structure of these representations that link proteins to their functional environment [182-184]. Although networks' static structure limits their capacity to depict the dynamism of many biological processes, they can also be used as templates for visualising and interpreting "omics" datasets. This includes how multiple partners interact and work together to open paths, as well as how the order in which things happen within a network can impact the functional result. Fine-grained connections between proteins and genes within the cell become particularly important in disease conditions where advantageous interactions and activities have been disrupted. Computational modelling enables researchers to study the system's evolving behaviour under different circumstances by carrying out in silico simulations and perturbations. A shift from static to dynamic, executable networks is necessary for a thorough system analysis [98,185-195].

8. Future perspectives, challenges in the diagnosis and treatment, and management in case of atherosclerosis

Developing a treatment approach for determining the risk of vulnerable plaque rupture in asymptomatic individuals is difficult since the idea of susceptible plaque is more complex than previously believed. First and foremost, noninvasive and intrusive techniques need to be able to identify the susceptible plaque. It is still impossible to clearly identify thin fibrous cap fibroatheroma, even though invasive and noninvasive imaging techniques have been demonstrated to predict the composition of coronary artery plaque, enabling real-time analysis and in vivo plaque characterisation. In addition, it is currently impossible to determine the degree of inflammatory infiltration of the cap, which surely plays a significant role in plaque disruption. Furthermore, real-time imaging techniques may not be able to identify dynamic plaque alterations, such as sudden intraplaque haemorrhages from the vasa vasorum, which may be crucial in predicting the danger of a plaque rupturing. Another difficulty is that the lesion-specific technique necessitates limiting the number of sensitive lesions and determining the number of susceptible plaques in each patient. However, this isn't the case. Multiple lipid-rich susceptible plaques have been seen in patients with fatal ACS or sudden cardiac death, according to several pathologic studies. Additionally, an analysis of data from several research revealed that mild to moderate stenosis is the precursor of coronary artery blockage and myocardial infarction 68% of the time. The third challenge is to document the natural history of the vulnerable plaque (in terms of the incidence of acute events) in patients receiving patient-specific systemic therapy. The

fourth challenge is to demonstrate that the approach significantly lowers the incidence of future events in comparison to the natural history. Neither is confirmed or recorded at this time. Fifth, we think that it is now impossible to predict which plaques are at risk of never rupturing. Even though we believe it is the great majority of them, we could need to change our attention to a more suitable therapy target. Furthermore, treating the vulnerable blood or myocardium in addition to the vulnerable plaque may be necessary to lower the risk of fatal events. It is anticipated that both preventive and therapeutic measures for atherosclerosis will affect the disease's fundamental pathogenetic pathways, including oxidative stress and inflammation. There is some evidence that calcium channel blockers and angiotensin-converting enzyme inhibitors (ACE-I), which are used in secondary prevention of atherosclerosis, have antioxidant properties and that their effects on vascular defence are connected to lower levels of oxidative stress.

9. Conclusions

Assessing the patient's overall vulnerability is more important than merely searching for a single, unstable plaque because atherosclerosis is a multisystemic, chronic inflammatory disease that affects the vascular, metabolic, and immune systems and has a wide range of local and systemic manifestations. Risk should be categorised using a composite vulnerability index score that incorporates blood vulnerability characteristics, the entire burden of atherosclerosis and vulnerable plaques in the aorta, coronary, carotid, and femoral arteries, and more. It goes without saying that employing the tools available today to develop such an index is challenging. It is challenging to identify high-risk individuals for acute vascular incidents before clinical symptoms appear. The greatest options for identifying diffuse active plaque at the moment include very sensitive inflammatory circulating markers like hs-CRP, cytokines, PAPP-A, and pentraxin 3, in addition to imaging techniques like MRI and ultrasound and local temperature sensors. In order to accomplish this, a concentrated effort is required to promote the use of the most promising tools and the creation of novel screening and diagnostic techniques for identifying individuals who are at risk.

Based on previous and current research and developments, we believe that there are certain restrictions to employing medicinal plants to prevent and treat atherosclerosis. The most significant aspect is that natural products offer a wide range of therapeutic benefits, making it nearly impossible to identify the precise mode of action that has been beneficial. This is particularly true in natural complexes, where plants can amplify or decrease each other's effects through a number of processes. It is impossible to monitor important outcome markers and negative consequences because practically all studies have a large number of constraints, but only a small portion of these are reported. Although there are rarely any standard criteria for recording side effects and interactions with prescription medications are rarely documented, most research claim that there are no negative effects. Medicinal plants that have shown atheroprotective efficacy in registered clinical trials and pleiotropic anti-atherosclerotic properties in experimental research are advised due to the significance of preventing atherosclerosis over the long term and lowering cardiovascular risk.

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Data Availability Statement: Not applicable.

Abbreviations: CAD: coronary artery disease; CVD: cardiovascular disease; ROS: Reactive oxygen species; H2O2: hydrogen peroxide; NF-kB: nuclear factor kappa B; HDL: high-density lipoprotein; WHO: World Health Organization; IMT: Intima-media thickness; SMCs: smooth muscle cells; MCs: muscle cells; LDL: Low-density lipoprotein; GPCR: G protein-coupled receptor; NO: Nitiric oxide; iNOS: inducible Nitric Oxide Synthase; VCAM-1: vascular adhesion molecule 1; MCP-1: monocyte chemotactic protein 1; IL-1: interleukin; TNF- α: tumor necrosis factor-α; ICAM-1: intercellular adhesion molecule 1; M-CSF: monocyte colony-stimulating factor; CRP: C-reactive protein; SR-A: scavenger receptor A; Ag: antigens; HSP: heat shock proteins; INSR: insulin receptor; RTK: receptor tyrosine kinases; IGF-IR: insulin-like growth factor I receptor; EGF: epidermal growth factor; VEGF: endothelial growth factor; Grb2: growth factor receptor-bound protein 2; Gab1: Grb2-associated binder 1; Shc: Src homology collagen-like; SHP2: SH2 domain-containing tyrosine phosphatase; JAK: Janus kinase; SH2B1: SH2b adapter protein 1; STAT3: signal transducer and activator of transcription 3; RACK1: receptor for activated C-kinase 1; STAT: signal transducer and activator of transcription; GEFs: guanosine exchange factors; GAPs: GTPase activating proteins; RGS: regulators of G protein signaling; PTP: protein tyrosine phosphatases; H2S: hydrogen sulfide; GPx: glutathione peroxidase;

GSH: glutathione; Prdx: peroxiredoxin; Srx: sulfiredoxin; NADPH: nicotine-amide adenine dinucleotide phosphate; PON2: paraoxonase 2; eNOS: endothelial nitric oxide synthase; PTX-3: pentraxin 3; Hs_CRP: high sensitive CRP; IGF-1: insulin-like growth factor 1; Lp-PLA2: lipoprotein-associated phospholipase A2; ADMA: asymmetric dimethylarginine; MPO: Myeloperoxidase; HMGR: 3-hydroxy-3-methylglutaryl CoA reductase; ACC: acetyl-CoA carboxylase; ACAT: acyl-CoA cholesterol acyltransferase; FAS: fatty acid synthase; G6PD: glucose-6-phosphate dehydrogenase; TC: total cholesterol; BMI: body mass index; AMAR: Atherosclerosis Monitoring and Atherogenicity Reduction; ET-1: Endothelin-1; TNF: Tumor necrosis factor; COX-2: Cyclooxygenase-2; PGI2: Prostacyclin; TGF-β: Transforming growth factor beta; TF: Tissue factor; FFAs: Free fatty acids; cIMT: Constraint-induced movement therapy.

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