THINK INDIA JOURNAL

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Botanicals for treatment of atherosclerosis

Rakshit Dhir[a], Naresh Singh Gill[c], Mukta Gupta[a,b]*

[a]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India

[b]Department of Pharmaceutical Sciences, I. K. Gujral Punjab Technical University, Kapurthala, Punjab, India

[c]Rayat Institute of Pharmacy, Railmajra, SBS Nagar, Punjab, India

*Corresponding Author E-mail: **mukta.16541@lpu.co.in**

ABSTRACT

Atherosclerosis is a large artery disease that leads to heart and stroke disease. It is characterized in the large arteries by the accumulation of lipids and fibrous elements. Atherosclerosis conventional treatments are statins, fibrates, niacin, and ezetimibe that work through various mechanisms. All these therapeutic agents are associated with one or more side effects, and none of the current therapies can accomplish the ultimate therapeutic target, i.e. they defend against atherosclerosis and reverse it partially. Herbal remedies are an alternative source of relieving symptoms of clinicians with atherosclerosis as well as addressing the risks associated with conventional methods of treatment. Approximately 80 percent of the world's population depends on herbal remedies because of more safety and less disadvantages reported by the World Health Organization (WHO). Herbal remedies are widely preferred to treat patients with atherosclerosis, as in many other diseases. Some of the important natural compounds reported to exhibit anti–atherosclerosis potential include tannins (*Terminalia arjuna*), thymoquinone (*Nigella Sativa*), polyphenols (*Astragalus membranaceus*), volatile oil (*Osimum basilicum*), saponins (*Panax notoginseng*). In present date, many researches are performed on medicinal, herbal and natural products globally for the treatment and prevention of atherosclerosis. Although a number of herbal medicines are recommended for Atherosclerosis, further research is required to investigate their safety, efficacy, and potential drug interactions.

Keywords: Disease modifying anti-atherosclerotic agents; herbal medicines; statins; fibrates; tannin; saponins; atherosclerosis

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

INTRODUCTION

Atherosclerosis is a progressive disease characterized by the accumulation in the large arteries of lipids and fibrous elements [1]. The word atherosclerosis is of Greek origin, which means intimate artery surface thickening and fat accumulation. In the central core of the plaque, fatty material is covered by a fibrous cap [2]. The term atherosclerosis consists of two parts, i.e. atherosis, meaning deposition of fat, macrophages whereas sclerosis means formation of fibrotic layer involving smooth muscle cells, leukocyte and connective tissue [3]. It is triggered by lipid deposition, oxidation of deposited fats and alteration which ultimately lead to thrombosis caused by chronic inflammation. One of the main triggers for atherosclerosis is hypercholesterolemia. Along with the same, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and lipoprotein (a) are other causative agents involved in pathophysiology of atherosclerosis [4].

Atherosclerosis starts to develop at the age course of 50, beginning in the early 13-19 age. It has been also suggested that in most of the cases the pathology of arterial lesion development lasts >40 years.

Globally, there were around 422.7 million prevalent cases of cardio vascular disorder and 17.92 million cases leads to deaths as per the data from 1990 to 2015 [5-6].

RISK FACTORS

- Unhealthy blood cholesterol level
- Diabetes
- Genetic
- Air Pollution
- Overweight
- High blood pressure

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

PATHOPHYSIOLOGY

The causative agents responsible for etiology of acute coronary syndromes involves hypercholesterolemia and atherosclerotic plaque rupture with luminal thrombosis which may further lead to sudden coronary failure [7]. Atherosclerosis is a complex series of events, which may share has symptoms similar to a chronic inflammatory process, hence, results in the formation of atherosclerotic plaque. The utmost step in the process is damage to the artery's endothelial cell, resulting in endothelial cell dysfunction. Endothelial cells attract leukocytes and smooth muscle of vascular cells, which grow in the wall of arteries and proliferate. This entire cellular component collectively leads to overproduction of amount of matrix of connective tissue and at the end; a mature fibrous plaque gets created [8].

In addition, the rise in plasma cholesterol levels results to alter arterial endothelial permeability that permits the relocation of lipids into the wall of arteries, particularly LDL-C particles. Circulating monocytes gets conferred to endothelial cells and results in expression of adhesion molecules such as vascular adhesion molecule-1 and selectins migrating by transferring into the sub-endothelial space. On getting loaded in the endothelial area, the monocytes attain the characteristics of the macrophage and get converted into foamy macrophages. On oxidation of LDL particles, these develop into potent chemo attractants in the sub-endothelial space. All these mechanism leads to accelerate the growth of large intracellular cholesterol by macrophages; therefore bind with native, altered lipoproteins and anionic phospholipids through the scavenger receptors (A, B1, CD36, CD68, for phosphatidylserine and oxidized LDL). The end result is a series of changes in the vascularity. Clinically atherosclerosis can be diagnosed by symptoms like contracting arteries and appearance of acute coronary syndromes owing to plaque instability [9].

CONVENTIONAL DRUGS USED FOR TREATMENT OF ATHEROSCLEROSIS

The goals of anti-atherosclerotic drugs currently used are to reduce triglyceride levels, LDL levels and inflammatory mediator inhibition along with alterations of certain receptors that are responsible for cholesterol synthesis and metabolism and ultimately improve patient life and expectation. Most of these targets were accomplished by adding non-steroidal anti-inflammatory

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

medications, calcium channel blockers, statins and fibrates.. The various classes of drugs used for treatment of Atherosclerosis along with their molecular targets and complications have been summarized in the Table 1.

Table 1: Therapeutic agents used in Atherosclerosis and their complications

Pharmacological class (drugs)	**Molecular target**	**Side Effects**	**References**
Statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, simvastatin)	HMG-CoA reductase	Urinary tract infection, diarrhea, stomach discomfort or pain	[10]
Fibrates (gemfibrozil, fenofibrate)	TG	Rash, itching, HSSD, impotence, blurred vision	[11]
NSAIDS (aspirin)	Phospholipase A_2	Gastrointestinal toxicity, kidney disease, reduce glomerular filtration rate,	[12, 13]
Steroids (hydrocortisone, Methylprednisolone, Beclamethosone)	Steroidal receptors	Electrolyte imbalance	[13]
Beta Blockers (propranolol, alprenolol, metoprolol, atenolol, pindolol, timolol)	Lipid deposition and arterial tissue hypoxia	Dry mouth, upset stomach, weakness, diarrhea/ constipation	[14,15]
Calcium Antagonists (verapamil, nifedipine, darodipine, iosradipine, diltiazem)	TG	Low blood pressure, flushing, edema, constipation.	[15]

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

vitamin (nicotinic acid or niacin)	TG, HDL	Nausea, diarrhea, leg cramps, muscle pain, insomnia.	[16]

NSAIDs: Non-steroidal anti-inflammatory drugs; HSSD: hypoactive sexual desire disorder; TC: total cholesterol; HDL: high density lipoprotein; TG: triglycerides

HERBAL PRODUCTS

Herbal products are used for various disorders worldwide. A number of natural products, including tannins, thymoquinone, polyphenols, saponins, salvianolic acid, polysaccharides, and extracts of certain herbal products, have anti-atherosclerotic activity and are therefore considered to be a gold mine for atherosclerosis treatment. They target serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, HMG CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) and affect different receptor functions.

Magnolol & Honokiol

Magnolol (*Mangnolia offinicalis*) has numerous biological activities such as anti-platelet aggregation, radical hydroxyl scavenging, Ca^{2+} -channel blocking and anti-inflammatory action [17]. Signal transducer and transcription protein activator 3(STAT3); a transcription factor and has major role in inflammatory responses and regulation of cell cycle by chemokines for example interleukin (IL)-6. *M. Officinalis* inhibited concentration-dependent effects on phosphorylation of Tyr705 and Ser727 which is induced by IL-6.[2] Thus, it has anti-inflammatory action. Honokiol; is biologically active component which is obtained from *M. officinalis*, significantly suppressed IL-6, IL-8 and MCP-1 development. The present study which aimed to examine the pharmacokinetics of magnolol after its oral administration in rats, and to determine its pharmacodynamic and pharmacokinetic properties showed the absorption $t_{1/2}$, the elimination $t_{1/2}$ and the maximum concentration founded to be 0·63 h, 2·33 h and 0·16 μg mL^{-1}, respectively. Oral bioavailability was about 4·9%, suggesting its potential in CVS disorders [18].

Cryptotanshinone

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Cryptotanshinone (CPT), a biologically active constituent obtained from Chinese herb *Salvia miltiorrhiza* bunge and has reported to possess anti-atherosclerotic activity and shows anti-tumor, anti-inflammatory and anti-Alzheimer's disease [19]. Oxidative stress caused by excessive ROS generation and inflammation caused by macrophage has crucial role in initiation, development and further advancement of endothelial dysfunction and hence leads to cardiovascular disease like atherosclerosis [2]. The oxidized form of LDL i.e. Ox-LDL which is caused by ROS, is the primary risk factor of atherosclerosis. CPT prevented the release of adhesion molecules at ox-LDL stimulation by controlling the regulated NF-πB pathway by lowering ROS production [19]. CPT significantly reduced creation of atherosclerotic plaque and ameliorates plaque stability by decreasing LOX-1 & MMP-9 expression and activating NF-πB. It has been further reported that CPT helps in treatment of CVS disorders by down-regulating pro-inflammatory mediators in the blood serum without any effect on serum lipid profile [2].

Salvianolic acid B

Salvianolic acid B (*Salvia miltiorrhiza* Bge); belongs to family Labiatae, is a phenolic acid component and has been used for treatment of number of diseases [20]. It is a potent water soluble antioxidant which targets Soluble P-selectin, NF-κB and its subunits, Intracellular adhesion molecule-1, IL-6, IL-8, MCP-1, PTX3, IκB and MCP-1 [20, 21].

Salvianolic acid B lowers JAK2 and STAT1 phosphorylation by persuading interferon-π (IFN-π). Monocyte adhesion to endothelial cells infected with IFN-π is also decreased with pretreatment of salvianolic acid B extract. This increases the protein blocker expression of activated STAT 1 and cytokine signaling suppressor 1 in endothelial cells. Salvianolic acid B also decreased adherence of ADP-activated platelets to endothelial cell line and alter NF-πB activation. The expression of m-RNA platelet regulated pro-inflammatory mediators was significantly lowered and further release of their corresponding proteins. Thus shows Inhibitory effects against proliferation and infiltration of VSMS [2].

Atractylenolides

Atractylenolides is a herb isolated from *Atractylodes macrocephala.* Atractylenolide inhibited dose-dependent proliferation and migration of Ox-LDL-induced VSMCs and decreased the

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

development of inflammatory cytokines and the expression of protein-1 (MCP-1) monocyte chemo attractant in VSMCs. It strongly inhibited activation of p38-MAPK and NF-πB. In addition, Atractylenolide prevented the development of foam cells in Ox-LDL mediated macrophages [22].

Esculetin

Esculetin, an effective non-competitive lipoxygenase blocker, extracted from *Artemisia scoparia* plant. Multiplication of VSMC has been shown to be inhibited. Esculetin suppressed dose-dependent MMP-9 which is generated by TNF- α in VSMC. The dosage of esculetin is 12.5-25 μg / ml [23]. It inhibit the activity of the promoter of TNF-α-induced MMP-9 and diminish the binding activities of the nuclear factor-πB (NF-μB) and the activator protein-1(AP-1), which are present in the promoter of the gene i.e MMP-9, in the VSMC treated with TNF-α. Thus, esculetin reduced cell migration and invasion by suppressing the expression of MMP-9, which subsequently reduces binding activities of AP-1 and NF-πB in VSMC treated with TNF-α [23].

Farrerol

Farrerol; commonly known as 'Man-shan-hong'; is isolated from the Chinese herb (*Rhododendron dauricum* L) and has effect on fetal bovine serum (FBS)-induced spreading of cultivated vascular smooth muscle cells [24]. It has remarkably inhibited the loss of cell viability induced by H_2O_2 & increased superoxide dismutase (SOD) along with glutathione peroxidase activities. In addition, Farrerol inhibited intracellular malondialdehyde (MDA) and reactive oxygen species (ROS) levels of H2O2-induced elevation [25].

Celastrol

Celastrol; a triterpenoid compound (*Tripterygium wilfordii Hook F)* exhibits various pharmacological activities like prevention of oxidative stress, inflammation, cancer and immunosuppression [26]. Celastrol remarkably shrink LDL-induced extreme expression of LOX-1 & formation of ROS and reduced the expression of LOX-1 & generation of superoxide [2]. Celastrol also meaningfully diminished LDL-induced expression of lectin which is induced by oxLDL like oxidized LOX-1 and prevented further generation of ROS. The possible

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

mechanism involved in anti-atherosclerotic effect of celastrol may be attributed to reduced level of IκB phosphorylation, iNOS, NO, and pro-inflammatory cytokines such as TNF-α and IL-6. Additionally it is further reported to reduce size of atherosclerotic plaque leading to its importance in atherosclerosis [26].

Isorhamnetin

Isorhamnetin; a bioactive compound and can be obtained from various plant sources such as *Hippophae rhamnoides* L., *Oenanthe javanica* and *Ginkgo biloba* L., and reported to possess numerous pharmacological activities including anti-cancer, anti-inflammatory, and anti-oxidant biological properties. It substantially inhibited oxLDL-induced macrophage damage by decreasing rates of ROS, lipid aggregation, and caspase activation. Isorhamnetin also promote the activation of phosphatidylinositol 3-kinase & the induction of heme oxygenase-1 which inhibit the progression of atherosclerotic plaque [2]. The serum concentrations of cholesterol and its subunits in blood were not remarkably improved by isorhamnetin treatment; thereby it is having atheroprotective effects [27].

β-Elemene

β-Elemene; sesquiterpenoid compound extracted from the essential oils of Chinese medicinal herb *Curcuma Wenyujin* [28]. β-Elemene has up-regulated antioxidant enzyme activity. Few of them are catalase, GPx and glutathione in aorta, thus leads to minimizing oxidative damage. Macrophage penetration was significantly reduced by β-elemene. It also reduced TC, TG, and LDL-C levels along with levels of TNF-α and IL-6 in invitro studies [29]. β-Elemene also increased NO generation and up-regulated eNOS phosphorylation [2].

Bisacurone

Bisacurone; a compound which is obtained from commonly used herb *curcuma longa* Linne (Zingiberaceae) and shows anti-atherosclerosis, anti-metastatic and anti-inflammatory effects [30]. It suppresses the expression of VCAM-1 and monocyte adhesion in endothelial cells [31]. Vascular cell adhesion molecule expression & NF-κB p65 translocate into nucleus and phosphorylation of IκBα, thus, it also act by suppressing the progression of inflammation,

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

vascular cell adhesion molecule expression and translocation of NF-κB p65 into its nucleus and phosphorylation of IκBα, therefore reduce the risk of complications in atherosclerotic patients.

Paeonol

Paeonol; having biological source *Paeonia lactiflora* shows both anti-atherosclerotic and anti-proliferation effects on smooth muscle cells [2, 32]. Paeonol influence phosphorylation of AMPK and retards phosphorylation of mTOR as well. It also potentially slows down ox-LDL-induced proliferation [33].

Astragaloside

Astragaloside IV is the most efficacious component extracted from *Astragalus membranaceus*, which widely used to treat cardiovascular disease such as atherosclerosis [34]. AS IV strongly suppressed platelet growth factor (PDGF) BB stimulated cell proliferation and migration of human dermal microvascular endothelial cells. AS IV inhibited the expression of associated proteins in the cell cycle by PDGF BB and down regulated the function of protein kinase mediated by p38 mitogen. It is therefore useful in treating atherosclerosis [35].

Artesunate

Artesunate; an herbal compound i.e. Sweet wormwood-derived primodial plant, has anti-inflammatory and anti-malarial activity [2]. It significantly reduces pro-inflammatory cytokine, such as TNF-α and IL-6. In addition, it may also control release of pro-inflammatory chemokines: IL-8 and MCP [36].

Corynoxetine

Corynoxeine (*Uncaria rhynchophylla);* a Chinese herb and has been used traditionally to treat atherosclerosis by exerting inhibitory effects on the proliferation of VSMC-induced platelet-derived growth factor (PDGF). The activation of PDGF-BB-induced extracellular signal-regulated kinase 1/2 by this drug has been substantially inhibited and beneficial in the prevention and treatment of atherosclerosis [37].

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

Sparstolonin B

Sparstolonin B; isocoumarin compound and can be obtained from different genus: *Sparganium stoloniferum* and *Scirpus yagara*. It reduces the activation of IL-1β and monocyte chemo attractant protein 1 in endothelial cells at both transcription and translation levels. It effectively suppressed the extracellular -signal-regulated kinase & act phosphorylation induced by LPS in HUVECs [38].

The various herbal products and their molecular targets has been **Table no. 2.**

Table 2: Herbal products with antiatheroscrotic potential along with their molecular targets

Component	Family	Chemical class	Source	Target	References
Bisacurone	Zingiberaceae	sesquiterpenoids	*Curcuma longa*	VCAM-1, NF-κB p65, IκB, Akt	[30]
β-Elemene	Zingiberaceae	sesquiterpenoids	*Curcuma Wenyujin*	IL-1β, TNF-α, INF-γ, MCP-1, ICAM-1, NO	[28]
Isorhamnetin	Ginkgoaceae	Flavonoid	*Hippophae rhamnoides* L.	OxLDL, ROS, PI3K, HO-1	[27]
Celastrol	Celastraceae	Triterpenoid	*Tripterygium wilfordii*	IκB, iNOS, NO, TNF-α, IL-6, OxLDL, LOX-1, ROS	[26]
Farrerol	Ericaceae	Flavonoid	*Rhododendron dauricum* L	NF-κB, COX-2, LOX-5,MMP-9, SOD, GSH-Px, MDA, ROS	[24]
Esculetin	Asteraceae	hydroxycoumarin	*Artemisia scoparia*	p42/44 MAPK, c-fos and c-jun	[2,23]
Atractylenolides	Asteraceae	sesquiterpene	*Atractylodes macrocephala*	ATP release, Ser473, phospho-	[2,22]

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

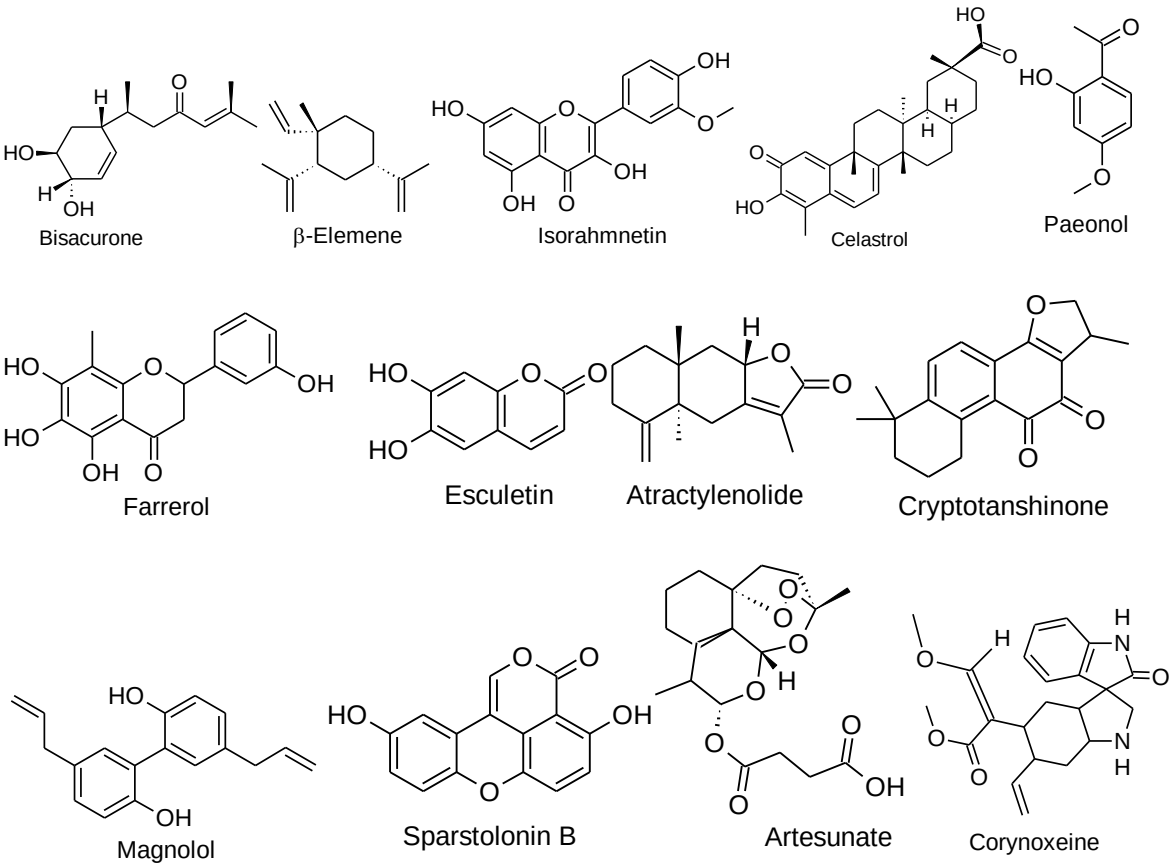
				p38	
Salvianolic acid B	Labiatae	phenolic acids	*Salvia miltiorrhiza*	MMP-2, MMP-9, JNK, NF-κB, ICAM-1, IL-1β, IL-6, IL-8	[20]
Cryptotanshinone	Labiatae	diterpene quinone	*Salvia miltiorrhiza*	LOX-1, MMP-9, ROS, NF-κB, ICAM-1, VCAM	[19]
Magnolol	Magnoliaceae	Biphenols	*Mangnolia offinicalis*	STAT3, ICAM-1, Tyr70, Ser727, cyclin D1, MCP-1	[17]
Paeonol	Paeoniaceae	Phenol	*Paeonia lactiflora*	ICAM-1, NF-κB, IκBα, p38, ERK	[2,32,33]
Astragaloside IV	Leguminosae	Triterpenoid	*Astragalus membranaceus*	TC, TG, LDL-C, HDL-C	[2,34]
Artesunate	Daisy	sesquiterpenoid	*Sweet wormwood*	TNF-α, IL-6, IL-8, MCP-1	[2,36]
Corynoxeine	Rubiaceae		*Uncaria rhynchophylla*	VSMCs, ERK1/2	[2,37]
Sparstolonin B	Typhaceae	Polyphenol	*Sparganium stoloniferum*	CCNE2, CDC6,	[38]

HO-1: heme oxygenase-I; ROS: reactive oxygen species;P13K: phosphatidyl-3-kinase; NF-KB: Nuclear factor kappa B cells MMP-9: matrix metalloproteinase-9; LOX: lipooxegenase; ICAM-1:Intracellular adhesion molecule-1; VSMC: vascular smooth muscle cells; TC: total cholesterol; TG: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; IL: interleukin; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule

The bioactive principles with antiatherosclerotic potential have been depicted in **Figure 1.**

ISSN: 0971-1260

Vol-22-Issue-17-September-2019



CONCLUSION

Although many conventional and non-conventional treatments for atherosclerosis have been identified, all of these are associated with few limitations such as long-term efficacy, safety, and cost. Herbal medicines relieve symptoms in atherosclerosis patients as well as to overcome the drawbacks associated with present treatment methods. Although a number of herbal medicines are recommended for atherosclerosis, further research is required to investigate their safety, efficacy, and potential drug interactions.

Refernece

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

1) A.J. Lusis, "Atherosclerosis," NIH, vol. 407, pp. 233-241, Sept. 2000.
2) J.Y. Kim and S.H. Shim, "Medicinal herbs effective against atherosclerosis: classification according to mechanism of action," Biomol. Ther., vol. 27, pp. 254-264, May 2019.
3) M. Setorki, M. Doudi, A. Baradaran and H. Nasri, "Atherosclerosis: process, indicators, risk factors and new hopes," Int. J. Prev. Med., vol. 5, pp. 927-946, Aug 2014.
4) S.C. Bergheanu, M.C. Bodde and J.W. Jukema, "Pathophysiology and treatment of atherosclerosis," Neth Heart J., vol. 25, pp. 231-242, Feb. 2017.
5) G.A. Roth, C. Jhonson, A. Abajobir, S. F. Abera and G. Abyu, "Global, regional and national burden of cardiovascular disease for 10 causes, 1990 to 2015," J. Am. Coll. Cardiol., vol. 70, pp. 1, July 2017.
6) J. R. Crouse, J. M. Toole, W. M. Mckinney, M. B. Dignan, F. R. Kahl and M. R. Mcmahan, "Risk factor for extracranial carotid artery atherosclerosis," pp. 990-995, Oct. 2019.
7) K. Sakakura and M. Nakano, "Pathophysiology of atherosclerosis plaque progression," Heart Lung Circ., vol. 23, pp. 387, April 2017.
8) M. E. Mitchell and A. N. Sidaway, "The pathophysiology of atherosclerosisa," J. Vasc. Surg., vol. 11, pp. 134-141, Sept 1998.
9) T. Head, S. Daunert and P. J. Goldschmit Clermont, "The aging andatherosclerosis: a fress look at arterial homeostasis," Front. Genet, vol. 8, Dec. 2017.
10) I. F. Charo and R. Taub, "Anti-inflamatory therapeutics for the treatment of atherosclerosis," Nat. Rev. Drug Discov., vol. 10, pp. 365-376, May 2011.
11) G. F. Watts and S.B. Dimmitt, "Fibrates, dyslipoproteinaemia and cardiovascular disease," Curr. Opin. Lipidol., vol. 10, pp. 561-574, Dec 1999.
12) M.C. Meyer, P. Rastogi, C.S. Becett and J. Mchowat, "Phospholipase A2 inhibitor as potential anti-inflamatory agents," Curr. Pharm, vol. 11, pp. 1301-312, 2005.
13) S. Wongrakpanich, A. wongrakpanich, K. Melhado and J. Rangaswami, "A comprehensive review of non- steroidal anti-inflamatory drugs use in the elderly," AGING DIS, vol. 9, pp. 143-150, Feb 2018.
14) G. Bondjers, "Anti-atherosclerotic effects of beta blockers," Eur. Heart J., vol. 15, pp. 8-15, Aug 1994.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

15) A. N. Orekhov, G. N. Baldenkov, V. V Tertov, L. H. Ryong, A. A. Lyakishev, V. A. Tkachuk and V. N. Smirnov, "Cardiovascular drugs and atherosclerosis: effects of calcium antagonists, beta-blockers and nitrates on atherosclerotic characteristics of human aortic cells," J. Cardiovasc. Pharmacol., vol. 12, pp. 66-68, 1998.

16) C. D. Meyers, V.S. Kamanna and M. L. Kashyap, "Niacin therapy in atherosclerosis," Curr. Opin. Lipidol., vol. 15, pp. 659-665, Dec. 2004.

17) J. H. C. Ho and C. Y. Hong, "Cardiovascular protection of magnolol: cell-type specificity and dose-related effects," J. Biomed. Sci., vol. 19, pp. 70, July 2012.

18) T. H. Tsai, C. J. Chou, T. F. Lee, L. C. H. Wang and C. F. Chen, "Pharmacokinetic and pharmacodynamic studies of magnolol after oral administration in rats," J. Pharm. Pharmacol., vol. 2, pp. 191-193, April 1996.

19) W. Zhao, C. Wu and X. Chen, "Cryptotanshinone inhibits oxidized LDL-induced adhesion molecule expression via ROS dependent NF-kB pathways," Cell Adhes. Migr., vol. 10, pp. 248-258, May 2016.

20) J. Wang, X. Xiong and B. Feng, "Cardiovascular effects of savianolic acid B," Evid. Based Compl. Alt., vol. 2013, pp. 16, Jun. 2013.

21) Y. H.Chen, S. J. Lin, H. H. Ku, M. S. Shaio, F. Y. Lin and J. W. Chen, "Savianolic acid B attenuated VCAM-1 and ICAM-1 expression in TNF treated human aortic endothielial cells,"J. Cell. Biochem., vol. 82, pp. 512-521, July 2001.

22) W. Li, W. Zhi, F. Liu, X. Wang and X. Niu, "Atractylenolide I restores OH-1 expression and inhibits Ox-LDL-induced VSMCs proliferation, migration and inflammatory response in vitro," Exp. Cell Res., vol. 353, pp. 26-34, Apr 2017.

23) S. J. Lee, U. S. Lee and W. J. Kim, "Inhibitory effects of esculetin on migration, invasion and matrix metalloproteinase-9 expression in TNF induced vascular smooth muscle cells," Mol. Med. Rep.,vol. 4, pp. 337-341, Mar. 2011.

24) Q.Y. Li, L. Chen, Y. H. Zhu, M. Zhang, Y. P. Wang and M. W. Wang, "Involvement of estrogen receptor in ferrerol inhibition of rat thoracic aorta vascular smooth muscle cell proliferation,"Acta Pharmacologica Sinica, vol. 32, pp. 433-440, Apr. 2011.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

25) Q. Liu, J. Li, A. H. Rose, J. Wang, J. Li, J. S. Janicki and D. Fan, "Chinese herbal compounds for the prevention and treatment of atherosclerosis: Experimental evidence and mechanisms," Evid. Based Compl. Alt., vol. 2014, pp. 15, Oct. 2014.

26) L. Gu, W. Bai, S. Li, Y. Zhang, Y. Han, Y. Gu, G. Meng, L. Xie, J. Wang, Y. Xiao, L. Shan, S. Zhou, L. Wei, A. Ferro and Y. Ji, "Celastrol prevents atherosclerosis via inhibiting LOX-1 and oxidative stress," Plos One, vol. 8, June 2013.

27) Y. Luo, G. Sun, X. Dong, M. Wang, M. Qin, Y. Yu and X. Sun, "Isorhamnetin attenuates atherosclerosis by inhibiting macrophage apoptosis via PI3/AKT activation and OH-1 induction," PLoS One, vol. 10, Mar 2015.

28) M. Liu, X. Chen, J. Ma, W. Hassan, H. Wu, J. Ling and, J. Shang, "B-Elemene attenuates atherosclerosis in apolipoprotein E-deficient mice via restoring NO levels and alleviating Oxidative stress" Biomed Pharmacother, vol. 95, pp. 1789-1798, Nov 2017.

29) Y. Zhong, J. Liu, W.M. Hou, W.L. Duan, X. Wang and J. Shang, "B-Elemene reduces the progression of atherosclerosis in rabbits," Chin. J. Nat. Med., vol. 13, pp. 415-420, Jun 2015.

30) D. Sun, I. T. Nizamutdinova, Y. M. Kim, X. F. Cia, J. J. Lee, S. S. Kang, "Bisacurone inhibits adhesion of inflammatory monocytes or cancer cells to endothelial cells through down-regulation of VCAM-1 expression," vol. 8, pp. 1272-1281, Sept 2008.

31) D. I. Sun, I. T. Nizamutdinova, Y. Minkim, X. F. Cai, J. Joonlee, S. Sikkang, Y. Shikkim, K. Munkang, G. Y. Chai, K, C. Chang and H. Jungkim, "Bisacurone inhibits adhesion of inflammatory monocytes or cancer cells to endothelial cells through down-regulation of VCAM-1 expression," Immunopharmacol, vol. 8, pp. 1272-1281, Sept. 2018.

32) H. Wu, A. Song and M. Dai, "The Anti-atherosclerotic Effect of Paeonol against Vascular Smooth Muscle Cell Proliferation by Up-regulation of Autophagy via the AMPK/mTOR Signaling Pathway," Front. Pharmacol., vol.4, pp. 948, Jan. 2018.

33) J. Wang, G. Wu, H. Chu, Z. Wu and J. Sun, "Paeonol Derivatives and Pharmacological Activities: A Review of Recent Progress,"Mini Rev. Med. Chem., vol. 15, pp. 1-6, Oct. 2015.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019

34) H. Qing, P. Liu and S. Lin, "Effects of Astragaloside IV on the SDF-1/CXCR4 Expression in Atherosclerosis of apoE−/− Mice Induced by Hyperlipaemia," J. Evidence Based Complementary Altern. Med, vol. 2015, pp. 1-8, Aug. 2014.

35) Z. Chen, Y. Cai, W. Zhang, X. Liu and X. Liu, "Astragaloside IV inhibits platelet-derived growth factor-BB-stimulated proliferation and migration of vascular smooth muscle cells via the inhibition of p38 MAPK signaling," Exp. Ther. Med, vol. 8, pp. 1253-1258, Oct. 2014.

36) W. Jiang, Y. Cen, Y. Song, P. Li, R. Qin, C. Liu, Y. Zhao and H. Zhou, "Artesunate attenuated progression of atherosclerosis lesion formation alone or combined with rosuvastatin through inhibition of pro-inflammatory cytokines and pro-inflammatory chemokines," Phytomedicine, vol. 23, pp. 1259-1266, Oct. 2016.

37) T. J. Kim, J. H. Lee, J. J. Lee, J. Y. Yu, B. Y. Hwang, S. K. Ye, L.Shujuan, L. Gao, M. Y. Pyo and Y. P. Yun, "Corynoxeine Isolated from the Hook of *Uncariarhynchophylla* Inhibits Rat Aortic Vascular Smooth Muscle Cell Proliferation through the Blocking of Extracellular Signal Regulated Kinase 1/2 Phosphorylation," Biol. Pharm. Bull, vol. 31, pp. 2073-2078, Nov. 2008.

38) Q. Liang, F. Yu, X. Cui, J. Duan, Q. Wu, P. Naragkatti and D. Fan, "Sparstolonin B suppresses lipopolysaccharide-induced inflammation in human umbilical vein endothelial cells, "Arch. Pharmacal. Res, vol. 36, pp.890-896, Jul. 2013.

ISSN: 0971-1260

Vol-22-Issue-17-September-2019