Review Article

Targeting Atherosclerotic Plaque in Avicenna’s View

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ABSTRACT

Objective: Cardiovascular disease (CVD) including atherosclerosis is currently the most common cause of death in the world. Atherosclerosis can be treated by a vast variety of modalities: from lifestyle modification to invasive open surgical bypass procedures. Regarding the limitations of conventional medicine, worldwide attention to complementary and alternative medicines has increased because of their holistic approach, lower cost and better public access. In this move towards Integrative Medicine -besides other traditional schools of medicine-Persian Medicine (PM) with its long historical background should be considered as a suitable source for research. Method: In this study we investigated major traditional literature of PM, Avicenna’s “Al-Qanun fi al-Tibb” [The Canon of medicine], to find suitable treatment modalities of atherosclerosis in comparison to conventional methods. Result: In the quest for a concept close to atherosclerosis, “sodde” (meaning obstruction) seems to be equal to atherosclerosis and “Mofateh” as opener drugs with different types including “Mohallelaat” (dissolvers) and “Moghatteaat” (cutting agents) have been recommended to remove the obstructing materials. Recent studies indicate that many of the medicinal herbs which were introduced as opener drugs by Avicenna have potential pharmacological effects on managing atherosclerosis. Conclusion: Scientific evidence confirm the efficacy of traditional herbs for elimination of atheroma. Anti-obstructive traditional medicines are similar to the conventional atherectomy by removing atherosclerotic plaque directly, but they are non-invasive, user-friendly, much cheaper and probably with less side effects.

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Traditionality

Medicine has a long background in Persian history. Avicenna (980-1037 AD) is the most eminent worldwide known Persian medicine physician and philosopher. Cardiovascular issues are widely discussed in the third volume of “al-Qanun fi al-Tibb” (the Canon of Medicine), “Kitab al-Adviyat al-Qalbiye” (The book on drugs for cardiovascular diseases) and “Resaley-e-Ragshenasi” (treatise on Pulsology) by Ibn Sina. Obstructive diseases have been important issues for Persian scholars for hundred years ago. One of the well-known diseases in Avicenna’s books is atherosclerosis which has been described with his scientific language as obstruction of vessels. He explained the general pathophysiological principles of obstruction and its treatment.

Background

Cardiovascular diseases (CVDs) are currently the first cause of death in the world. Atherosclerosis is its most common subdivision which causes other CVDs including coronary heart, cerebrovascular and peripheral arterial diseases [1, 2]. Atherosclerosis is a dynamic and complex
inflammatory disease that its first stage is fatty streak formation (Figure 1). This lesion often progresses into fibrous plaques which may be ruptured leading to thrombosis [2-5]. Atherosclerosis therapy includes a vast range of modalities beginning from lifestyle modification and medical therapy to more semi-invasive percutaneous endovascular interventions up to invasive open surgical bypass procedures or combination of these approaches. Each of these modalities has their own advantages and disadvantages [6-9].

Figure 1: Persian traditional medicine recommends “Mofatehaat” as opener drugs to remove the obstructing materials.

The most commonly used drugs include lipid lowering, antiplatelet, beta-blockers and drugs acting on the renin-angiotensin-aldosterone system (RAAS) for primary and secondary prevention and for treatment of acute coronary syndromes nitrates, fibrinolytics, antithrombins and intravenous antiplatelet drugs are consumed [6, 7, 10]. In addition, based on risk factors existing in different patients, other medications such as antihypertensive and antihyperglycemics may also be used [11]. Available drugs, besides having side effects, are mainly designed to prevent formation or progression of atheroma/clots, and according to our best knowledge, none can eliminate existing atheroma [10].

Regarding the limitations of conventional medicine, worldwide attention to the complementary and alternative medicines (CAM) has increased because of their holistic approach; lower cost and better public access [17, 18]. Integrating proven traditional treatments with conventional medicine is currently encouraged by The World Health Organization [19]. In this move towards Integrative Medicine -besides other traditional schools of medicine-Persian Medicine (PM) with its long historical background should be considered as a suitable and perfect source for research in complementary and alternative medicine. In this study we investigated major traditional literature of PM to find suitable treatment of atherosclerosis in comparison to the conventional methods.

Methods

In this study, the most prominent source of traditional Persian medicine (TPM), Avicenna’s “Al-Qanun fi Al-Tibb” [The Canon of medicine] was searched for equivalent (Farsi and Arabic) words for obstruction and also anti-obstruction drugs. The general pathophysiological principles of obstruction, its treatment and herbal medicines were extracted and classified. A parallel search in data bases was done by using the key words of atherosclerosis and related pharmacological effects. Finally, the traditional and current mainstream paradigms of atherosclerosis treatment were compared.

Historical Background

Medicine has a long background in Iranian history. In Avesta, the oldest Iranian historical and religious text, five classes of physicians are mentioned. “Ashou bishazu” (health practitioner) who heals with hygiene, “Data bishazu” (Forensic Medicine) who works with law, “Kareto bishazu” (surgeon) who uses surgical blade for treatment, “Orvaru bishazu” (herbal physician) who treats with herbs and “Mantra bishazu” (Psychotherapist) who cure with holy words. Archaeological findings also confirm the existence of these five medical groups in ancient Persia [20]. In ancient Persia (600 BC-652 AD), medical paradigm based on the humoral theory was prevalent. Pahlavi texts from the Sassanid era (224 to 651 AD) show that scientists and physicians of that period were familiar with cardiovascular physiology and diseases such as the role of blood in feeding organs, description of pulmonary circulation, spreading infection by blood through the body and stroke [21, 22]. In the Islamic era (from seventh century AD), great Iranian scholars wrote important literatures in various fields of medicine and pharmacy. They collected and enriched various literatures from Rome, Greece, ancient Persia and India [23]. Cardiovascular diseases and their prevention and treatment is one of the major research topics of scientists of this period of medicine history [24, 25].

Although Avicenna’s view in many cases is similar to Galen’s, the most prominent Greek scholar, he also presented his own opinions, systematized the science of medicine and developed new theories in his works. Therefore, Avicenna is the most eminent worldwide known PM physician and philosopher [23, 24]. Cardiovascular issues are widely discussed in the third volume of “al-Qinun fi al-Tibb” (The Canon of Medicine), “Kitab al-Adviyat al-Qalbiye” (The book on drugs for cardiovascular diseases) and “Resaley-e-Ragshenasi” (treatise on Pulsology) by Ibn Sina [24], Leonardo Da Vinci (1452-1519 AD) is said to be one of the first who described atherosclerosis and after that Caleb Hillier Parry (1755-1822 AD) during his studies discovered a plaster-like substance in arteries nevertheless, obstructive diseases have been important issues for Persian scholars for hundred years ago [26]. One of the well-known diseases in Avicenna’s books (980-1037 AD), is atherosclerosis which, has been described with his scientific language as obstruction of vessels [27].

Atherosclerosis in Canon of Medicine

I Definition and Causes of Atherosclerosis (Sodde Orough)

In the quest for a concept close to atherosclerosis in Canon of Medicine, the most comparable term seems to be “sodde” meaning obstruction [27, 28]. Accumulation of materials in the vessels which prevents blood to
reach the organs is called vessel obstruction “sodde orough”. Although it has been mentioned to occur in all parts of the body such as liver, spleen, kidneys, nose, nerves, brain, heart, eyes, intestines and etc., Avicenna believed that the obstruction of heart, brain and liver arteries are the most acute ones [29]. In the third volume of the Canon, he described that arterial obstruction of heart and brain can lead to myocardial infarction and stroke, respectively [30].

Avicenna used the theory of humoral medicine to explain the causes of vascular obstruction. In Persian medicine humors includes phlegm or “balgham”, blood or “dam”, yellow bile or “safra” and black bile or “sauda”. Imbalance in the quantity and quality of these natural humors can lead to abnormal humors production and causing different diseases [31, 32]. Abnormal phlegm humor, deposition of abnormal black bile in the artery wall, yellow bile and black bile imbalance are related to cardiovascular disease risk factors and atherosclerosis [33-35]. Avicenna believes that abnormal dense “Ghaleez” or viscose “Lazej” humors accumulation is the most important cause of obstruction. The difference between dense and viscose humor in physical features is like the difference between clay and melted glue [29, 31, 36, 37]. From a holistic view, formation of fatty streak and vascular calcification which involves the process of atherosclerotic plaque progress can be consider as viscose and dense humors respectively.

II Atherosclerosis Treatment by Opener Drugs (Mofattehaat)

To eliminate the waste materials from body they should have optimum physical properties. So, dense matter must get more fluid, and the viscous adhesive matter must be degraded into smaller pieces [31]. Certain drugs generally named openers- “Mofattehaat”: were used to remove the obstructing materials. Basically, openers with different types of functions are used according to the nature of the accumulated material to alter their rheological properties. For dense humors, dissolvers named “Mohallelaat” are used and for viscose humors, cutting agents or shredders named “Moghatteaan” are consumed [29, 38]. The "Mohallel" or dissolver is a drug that separates, dilutes and evaporates the stored humor by its hot nature [38]. This heat for removing obstructive material should be optimum, not too high nor too low. Excessive heat increases material thickness by dehydration and insufficient heat may not be effective [29]. The “Mohatte” or cutting agent / shredder is a medicine that penetrates easily into the particles. Cutting agent, due to its lower density, not only separates the viscous humor from the attached surface but also divides it to smaller fragments, therefore facilitates their removal [38]. Avicenna has introduced many herbal medicines as “Mofateh” in the second volume of the Canon of medicine [38]. He describes the opener function of some medicines in general and for some of them he mentions the organ in which they have anti-obstructive effect. For example, the opening function of bitter almond is more than sweet almond and chicory opens the obstruction of organs and vessels [38].

Nowadays, management of atherosclerosis is carried out through modification of risk factors and processes involved in its pathogenesis such as Oxidation, inflammation, dyslipidemia, diabetes, endothelial dysfunction, platelet aggregation [39]. Table 1 presents opener drugs from Canon of medicine with examined pharmacological effects contributed in atherosclerosis treatment. It shows that many medicinal plants families can affect obstructive diseases. But Lamiacaeae, Apiaicaeae and Asteraceae are the main referred families. Many in vivo, in vitro and clinical trial studies have been carried out on different functions of these herbs which can prove their opener effect. Most of them have anti-oxidant, Anti-dyslipidemia (by decreasing cholesterol, triglyceride, LDL and increasing HDL), anti-hyperglycemic and anti-inflammatory effects.

Table 1: Medicinal plants mentioned in the Canon of medicine as anti-obstruction treatment.

| Scientific name          | Common name | Traditional name | Family      | Pharmacological effects                                      | Ref. |
|--------------------------|-------------|------------------|-------------|--------------------------------------------------------------|------|
| Pimpinella anisum L.     | Anise       | Anison           | Apiaceae    | Anti-oxidant *(in vitro, in vivo)*, Anti-inflammatory *(in vivo)*, Anti-hypertensive *(in vivo)*, Bradycardia *(in vivo)*, Anti-dyslipidemia *(in vivo)*, Anti-diabetic *(in vivo)*, Hepatoprotective *(in vitro, in vivo)* | [40-44] |
| Tanacetum parthenium (L.) Sch.Bip. | Feverfew     | Aghovan          | Asteraceae  | Anti-oxidant *(in vitro, in vivo)*, Anti-dyslipidemia *(in vivo)*, Hepatoprotective *(in vivo)* | [45-47] |
| Lavandula stoechas L.    | Lavender     | Ostokhoddus      | Lamiaceae   | Anti-oxidant *(in vitro)*, Anti-inflammatory *(in vitro)*, Anti-insulin resistant *(in vitro, in vivo)* | [48-50] |
| Moringa oleifera Lam     | Moringa     | Ban              | Moringaceae | Anti-oxidant *(in vitro, in vivo)*, Anti-inflammatory *(in vitro, in vivo)*, Anti-dyslipidemia *(in vivo)*, Anti-diabetic *(in vivo)*, Anti-obesity *(in vivo)*, Anti-coagulant and anti-platelet aggregation *(in vitro)*, Hepatoprotective *(in vivo)* | [51-58] |
| Matricaria chamomilla    | Chamomile   | Babunaj          | Asteraceae  | Anti-oxidant *(in vitro, in vivo)*, Anti-dyslipidemia *(in vivo)*, Anti-hyperglycemic *(in vivo)*, Anti-obesity *(in vivo)* | [59, 60] |
| Plant Name                          | Common Name          | Family           | Characteristics                                                                 |
|------------------------------------|----------------------|------------------|---------------------------------------------------------------------------------|
| Melissa officinalis L.             | Lemon Balm           | Lamiaceae        | Anti-platelet aggregation (*in vitro*), Anti-dyslipidemia (*in vivo*), Cardiovascular effects (*human study*), Anti-hypertensive (*human study*), Hepatoprotective (*in vivo*) |
| Adiantum capillus veneris L.       | Maidenhair Fern      | Pteridaceae      | Anti-inflammatory (*in vitro, in vivo*)                                        |
| Ficus carica L.                    | Common Fig           | Moraceae         | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anti-diabetic (*in vitro, in vivo*), Anti-obesity (*in vitro*), Anti-hypertensive (*in vitro, in vivo*), Decreasing heart rate (*in vitro, in vivo*), Hepatoprotective (*in vivo*) |
| Gentiana latea L.                  | Great Yellow Gentian | Gentianaceae     | Anti-oxidant (*in vitro*), Anti-inflammatory (*in vitro*), Anti-migratory (*in vitro*) |
| Teucrium polium L.                 | Betty Germander      | Lamiaceae        | Anti-oxidant (*in vivo*), Anti-dyslipidemia (*in vivo*), Anti-diabetic (*in vivo*), Positive inotropic on the heart (*in vivo*), Anti-hypertensive (*in vivo*), Vasorelaxant (*in vivo*), Improving endothelial dysfunction (*in vivo*), Improving vascular inflammation (*in vivo*) |
| Ocimum gratissimum L.              | Clove Basil          | Lamiaceae        | Anti-oxidant (*in vitro*), Anti-diabetic (*in vivo*), Anti-hypertensive (*in vitro, in vivo*) |
| Lawsonia inermis L.                | Henna                | Lythraceae       | Anti-oxidant (*in vitro*), Anti-dyslipidemia (*in vivo*), Anti-diabetic (*in vivo*), Anti-thrombotic (*in vitro*), Hepatoprotective (*in vivo*) |
| Foeniculum vulgare Miller         | Fennel               | Apiaceae         | Anti-oxidant (*in vitro*), Anti-inflammatory (*in vitro, in vivo*), Anti-diabetic (*in vivo*), Anti-hypertensive (*in vitro*), Hepatoprotective (*in vivo*) |
| Crocus sativus L.                  | Saffron              | Iridaceae        | Anti-oxidant (*in vitro, in vivo*), Anti-inflammatory (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anti-diabetic (*in vivo*), Anti-hypertensive (*in vivo*) |
| Nardostachys jatamansi DC          | Spikenard            | Caprifoliaceae   | Anti-oxidant (*in vitro*), Anti-inflammatory (*in vitro*), Anti-hyperglycemic (*in vitro*), Anti-hypertensive (*in vitro*), Hepatoprotective (*in vivo*) |
| Anethum graveolens L.              | Dill                 | Apiaceae         | Anti-oxidant (*in vitro*), Anti-inflammatory (*human study*), Anti-dyslipidemia (*in vivo, human study*), Anti-diabetic (*in vivo, human study*) |
| Aloe vera L.                       | Aloe                 | Asphodelaceae    | Anti-oxidant (*in vitro*), Anti-inflammatory (*in vitro, in vivo*), Anti-dyslipidemia (*in vitro, in vivo*), Anti-diabetic (*in vitro, in vivo*), Anti-obesity (*in vivo*), Prevention of vascular calcification of vascular smooth muscle cells (*in vitro, in vivo*), Hepatoprotective (*in vivo*) |
| Taraxacum officinalis Weber        | Dandelion            | Asteraceae       | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anticoagulant and anti-platelet activity (*in vitro*) |
| Species                        | Common Name       | Family               | Activities                                                                                   | References       |
|-------------------------------|-------------------|----------------------|---------------------------------------------------------------------------------------------|------------------|
| Juniperus oxycedrus L.        | Cade              | Cupressaceae         | Anti-oxidant (*in vitro, in vivo*), Anti-hyperglycemic (*in vivo*)                          | [97-99]          |
| Marrubium vulgar L.            | White Horehound   | Lamiaceae            | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anti-diabetic, (*in vivo*), Hepatoprotective (*in vivo*) | [100-103]        |
| Pistacia vera L.              | Pistachio         | Anacardiaceae        | Anti-oxidant (*in vitro, human study*), Anti-inflammatory (human study), Anti-dyslipidemia (human study), Anti-diabetic (human study) | [104, 105]       |
| Rubia tinctorum L.            | Rose Madder       | Rubiaceae            | Anti-platelet aggregation (*in vitro, in vivo*)                                             | [1106]           |
| Capparis spinos L.            | Caper             | Capparaceae          | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (human study), Anti-diabetic (in vivo, human study), Hepatoprotective (in vivo) | [1107-109]       |
| Apium graveolens L.           | Celery            | Apiaceae             | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anti-hyperglycemia (*in vivo*), Vasodilator (*in vivo*), Decrease heart rate (*in vivo*), Anti-hypertensive (*in vivo*) | [110-112]        |
| Cuscuta chinensis Lim.        | Chinese Dodder    | Convolvulaceae       | Anti-oxidant (*in vitro*), Anti-diabetic (*in vivo*), Cardio protective (*in vivo*), Hepatoprotective (*in vivo*) | [1113]           |
| Plantago major L.             | Broadleaf Plantain| plantaginaceae       | Anti-oxidant (*in vitro, in vivo*), Anti-hyperglycemic (*in vivo*), Anti-dyslipidemia (*in vivo*), Hepatoprotective (*in vivo*) | [114-116]        |
| Prunus dulcis                 | Almond            | Rosaceae             | Anti-oxidant (*in vitro*), Anti-inflammatory (*in vivo*), Anti-dyslipidemia (*in vivo, human study*), improving vascular endothelial function (*in vivo*), Hepatoprotective (*in vivo*) | [117-122]        |
| Commiphora myrrha (Nees) Engl. | Myrrh             | Burseraceae          | Anti-oxidant (*in vitro*)                                                                 | [1123]           |
| Origanum majorana L.          | Majoram           | Lamiaceae            | Anti-oxidant (*in vitro, in vivo*), Anti-inflammatory (*in vivo*), Anti-dyslipidemia (*in vivo*), Anti-platelet activities (*in vitro*), Preventing proliferation of vascular smooth muscle cells (*in vivo*), Hepatoprotective (*in vivo*) | [114-127]        |
| Trachyspermum ammi (L.) Sprague ex Turrill | Ajwain          | Apiaceae             | Antioxidant (*in vitro*), Anti-inflammatory (*in vivo*), Anti-dyslipidemia (*in vivo*), Anti-platelet aggregation (*in vitro*), Anti-hypertensive (*in vivo*), Bradycardia (*in vivo*) | [1128, 129]      |
| Acorus calamus L.             | Sweet Flag        | Araceae              | Anti-dyslipidemia (*in vivo*), Anti-diabetic (*in vitro, in vivo*)                          | [1130, 131]      |
| Hypericum perforatum L.       | Perforate St John's-Wort | Hypericaceae       | Anti-diabetic (*in vivo*)                                                                  | [1132]           |
| Cichorium intybus L.          | Chicory           | Asteraceae           | Anti-oxidant (*in vitro, in vivo*), Anti-inflammatory (*in vitro, in vivo*), Anti-dyslipidemia (*in vivo*), Anti-hyperglycemic (*in vivo*), Endothelium dependent vasodilation (*in vivo*), Anti-platelet aggregation (human study), Hepatoprotective (*in vivo*), Anti-hypertension (*in vivo*) | [1133-137]       |
| Asparagus officinalis L.      | Asparagus         | Asparagaceae         | Anti-oxidant (*in vitro, in vivo*), Anti-dyslipidemia (human study), Anti-hyperglycemic (*in vivo, human study*) | [1138, 139]      |
Discussion

Presentation of large number of medicinal plants as opener drugs demonstrates importance of treating obstructive diseases in Persian medicine. Recent studies indicate that many of the medicinal plants which were introduced as opener drugs by Avicenna have potential pharmacological effects on managing atherosclerosis. In addition, there are studies showing the direct effect of some of these herbal medicines on decreasing and removing atherosclerotic plaque.

The effect of Moringa oleifera leaf extract on reduction of atherosclerotic plaque formation on the internal carotid artery wall has been indicated in cholesterol fed rabbits [12]. Supplementation of 2% Gentiana lutea root powder in streptozotocin induced diabetic rats reduced the thickness of medial layer in aortic wall, collagen deposition and lipid and foam cell accumulation [30]. Saffron aqueous extract decreased the atherosclerotic lesion size and favorable alterations in plaque texture and enhancement of plaque stability in (ApoE-/-) mice [43].

An in vivo study by Choi et al. on high cholesterol fed rabbits indicated that Taraxacum officinale root or leaf administration decreased the atherosclerotic plaque formation in aortic walls [56]. Chicory consumption suppressed aortic cholesterol accumulation, reduced atherosclerotic lesion area and improved its stability by decreasing macrophage accumulation and increasing collagen content in ApoE-/- mice with pre-established atherosclerosis [95]. Cichorium intybus is traditionally used for blood cleansing, high blood pressure, blood purification and arteriosclerosis in Italy [140]. Yan-Sheng-Yin (YSY), a Chinese natural dietary supplement, composed of six plants which celery is its main ingredient. The ApoE-KO mice model of hyperlipidaemia was used to investigate the effects of YSY on hyperlipidaemia, atherogenesis, and obesity. The results showed reduction of visceral adipose tissues mass and adipocyte size. Also, high-dose YSY treatment decreased hepatic steatosis and atherosclerosis [141]. Amygdalin is an abundant component in almonds. Amygdalin has hypolipidemic and anti-inflammatory effect in (ApoE-/-) mice.

In atherosclerosis situation the diameter of aortic sinus and plaque area increases and the lumen area decreases which amygdalin administration improves them. D. Jiagang et al. in their study observed increase of DNA fragmentation and apoptotic cells in atherosclerotic lesions of treated animal models so they hypothesized decreasing atherosclerosis by apoptosis [83]. In addition to the effects of some herbs on removing atherosclerotic plaque, there are also invasive treatments for this purpose. Atherectomy is a potential semi-invasive method for debulking and removing accumulated materials from the vessels directly [16]. Laser atherectomy uses ultra-violet (UV) light to break carbon-carbon bonds. In this method, large molecules and water absorb energy and thus heated up and intracellular liquid is vaporized. Finally, the accumulated materials are destroyed. This process, also named as photo ablation, leads to dissolution and vaporization of the atherosclerotic plaque [142-144]. Different sharp cutting devices are also used to remove plaques from arterial walls in directional (DA), rotational (RA) and Orbital atherectomy (OA) methods [145-148].

As mentioned, in TPM dissolving and cutting method is used for removing accumulated material. Generally, it seems that dissolver drugs “mohallelaat” may resemble the laser atherectomy technique where in both, the accumulated material is removed by some sort of energy either from the hot nature or UV light leading to vaporization of the obstructing material. Traditional cutting agents “moghatteaat” may be comparable to directional, rotational and orbital atherectomy where they all concentrate on the fragmentation of the attached substance by using incising means. Although, anti-obstructive traditional medicines are similar to atherectomy technique in targeting atheroma, but certainly drug therapy is preferred to invasive interventions.

Conclusion

In summary, atherosclerosis is a chronic disease which must be prevented and treated over time to prevent acute illnesses such as heart attack and stroke. Therefore, consumption of complementary therapies becomes important. CAM is noninvasive, user-friendly and has lower costs and probably less side effects in comparison to conventional therapies. By considering scientific evidence which confirms the use of traditional herbs to eliminate atheroma specifically, it is hoped that by further related researches, effective drugs could be developed from traditional Persian medicine to remove the atheroma, making better success in the treatment of atherosclerosis.

Highlight

i. In Avicenna’s viewpoint “obstruction” seems to be equivalent to atherosclerosis.
ii. Anti-obstructive drugs are known as “openers”, in Avicenna’s viewpoint.
iii. Scientific evidences confirm the efficacy of openers for elimination of atheroma.

Conflicts of Interest

None.

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