

Exploring Alternative Medicines in the Treatment of Atherosclerosis: an Insight into Molecular Aspect

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ABSTRAK

Malaysia diberkati kerana mempunyai beberapa produk semulajadi. Sejak dekad yang lalu, kajian telah dijalankan untuk menemui suplemen anti-aterosklerosis yang sangat berkesan. Phytoestrogen, iaitu protein soya, telah mendapat banyak perhatian, selama bertahun-tahun. Beberapa literatur phytoestrogen telah menekankan kesan terapeutik ubat-ubatan alternatif terhadap aterosklerosis. Walau bagaimanapun, mekanisme anti-aterosklerosis keseluruhan isoflavon tanpa mengira keadaan menopause atau postmenopausal belum dibincangkan setakat ini. Kajian ini bertujuan untuk merumuskan mekanisme molekul pelbagai jenis ubat alternatif untuk rawatan aterosklerosis pada populasi umum. Herba yang biasa digunakan dalam rawatan aterosklerosis ialah bawang putih (*Allium sativum*), buah delima (*Punica granatum*), halia (*Zingiber officinale*), kayu manis (*Cinnamomum spp.*) dan teh hijau (*Camellia sinenses*). Walau bagaimanapun, minyak kelapa sawit, minyak kelapa sawit, minyak zaitun dan omega-3 juga memainkan peranan penting dalam mengurangkan risiko aterosklerosis dengan menurunkan tahap LDL, meningkatkan endothelial nitric oxide synthase (eNOS), menghancurkan radikal bebas dan juga mengurangkan proses keradangan. Daidzein meningkatkan perubahan aterosklerotik dengan mengaktifkan laluan NF- κ B dan mengawal pernyataan sitokin radang. Genistein mengurangkan sel-sel monocytes-endothelial dan rembesan molekul melekat melalui laluan cAMP / PKA, ia mengurangkan tindak balas keradangan melalui permulaan faktor nukleus faktor faktor nikel 2 (Nrf2) / heme oxygenase-1 (HO-1). Secara keseluruhannya, kami menyedari bahawa ubat alternatif menunjukkan keberkesanan terapeutik yang luar biasa untuk rawatan aterosklerosis pada pesakit daripada pelbagai usia.

Kata kunci: aterosklerosis, mekanisme, molekul, ubat alternatif

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ABSTRACT

Malaysia is blessed to have several natural products. Since past decades, studies have been carried out to discover the highly effective anti-atherosclerotic supplements. The phytoestrogens and soy proteins have gained much attention, over the years. Several literature highlighted the therapeutic effect of alternative medicines on atherosclerosis. However, the overall anti-atherosclerotic mechanism of isoflavones regardless of menopause or postmenopausal state was not discussed, to date. This review aimed to summarize the molecular mechanism of different types of alternative medicines for the treatment of atherosclerosis in general population. The herbs commonly used in the treatment of atherosclerosis are garlic (*Allium sativum*), pomegranate (*Punica granatum*), ginger (*Zingiber officinale*), cinnamon (*Cinnamomum spp.*) and green tea (*Camellia sinenses*). Nevertheless, the palm oil, coconut oil, olive oil and omega-3 also plays significant role in attenuating the risk of atherosclerosis by decreasing the LDL level, increasing the endothelial nitric oxide synthase (eNOS), scavenging the free radicals and also decreasing the inflammatory process. Daidzein improves atherosclerotic changes by activating the NF- κ B pathway and regulating the expression of inflammatory cytokines. Genistein reduces the monocyte-endothelial cell and adhesion molecules secretion via cAMP/PKA pathway, it decreases the inflammatory response via initiation of nuclear factor erythroid 2-related factor (Nrf2)/ heme oxygenase-1 (HO-1) pathway. Conclusively, we recognized that alternative medicines demonstrate remarkable therapeutic efficacy for the treatment of atherosclerosis in patients of all ages.

Keywords: alternative medicine, atherosclerosis, molecular, mechanism

INTRODUCTION

Atherosclerosis is considered to be a chronic arterial disease and leading cause of death globally, including Malaysia. Atherosclerosis remains a complex multifocal disease as it affects the arterial blood vessels via deposition of cholesterol plaques in the arterial walls. The process starts with the formation of fatty streaks in the arterial walls which gradually develop into the atheroma. The atheromatous plaques then invade and accumulate in the form of macrophages. The increase in

deposition of macrophages results in local thrombosis and eventually causes partial or total blockage of the affected artery. Apart from cholesterol residues, calcium and other crystallized materials deposited in the plaque eventually hardens the affected artery and its elasticity is lost (Sakaruka et al. 2013; Xiao-Hua et al. 2013). In year 2012, the World Health Organization (WHO) reported that there was more than 20% mortality in 100,000 populations in Malaysia (WHO 2015). According to the data, Chinese ethnic race had increase in prevalence to develop

atherosclerosis who were at high risk of hypertension and hyperlipidaemia compared to the other ethnic groups. This was probably because of lifestyle differences. However, improving lifestyle changes solely was not enough to reduce the prevalence of the disease.

Hence, the modern or synthetic medications played a crucial role in the treatment of atherosclerosis. At present, statins and niacin are the commonly used drugs in lowering the low-density lipoprotein (LDL) and regulating the atherosclerotic process (Wadhera et al. 2016). It causes decrease in the LDL level, increase the high-density lipoprotein (HDL) level and lowers the level of triglycerides (Goedeke et al. 2016). However, it was found to possess certain side effects such as high blood sugar and delirium. Moreover, statin was contraindicated in pregnant women and diabetic patients. Therefore, there is a need to find an alternative supplement which has less side effects and has good efficacy in the treatment of atherosclerosis.

Since past few decades, several studies were conducted on the herbs and complementary medicine for the treatment of atherosclerosis. The herbs commonly used in the treatment of atherosclerosis are garlic (*Allium sativum*), pomegranate (*Punica granatum*), ginger (*Zingiber officinale*), cinnamon (*Cinnamomum spp.*) and green tea (*Camellia sinenses*). Nevertheless, the palm oil, coconut oil, olive oil and omega-3 also plays significant roles in attenuating the risk of atherosclerosis. These natural medicines are known to possess certain active compounds or phenolic

agents. According to *in vivo* and also *in vitro* studies, it was reported that the active ingredients present in natural products are able to decrease the LDL level, increase the nitric oxide (NO), scavenge the free radicals and also decrease the inflammatory process (Al-Shehabi et al. 2016).

Besides herbs and oils, a number of studies reported the beneficial properties of isoflavones, on various type of cells such as endothelial cells, vascular smooth muscle cells and extracellular matrix. Isoflavones are plant derived compounds mostly found in soy protein. It was observed that isoflavones decrease the arterial stiffness and increase NO production in regulating the atherosclerosis (Al-Shehabi et al. 2016; Sirotkin & Harrath 2014; Wang et al. 2013). Isoflavones also revert the pathophysiology of atherosclerosis by decreasing the levels of LDL, angiogenesis, inflammation and reactive oxygen species (ROS). Epidemiological studies showed consumption of soy protein reduces the endothelial cells dysfunction at the early stage of the disease (Gencel et al. 2012; Gil-Izquierdo et al. 2012). Daidzein, the active compound found in soy protein, attenuates the endothelial cells dysfunction in diabetes mellitus was reported, recently (Park et al. 2013). However, the summarised findings on the molecular effect of alternative medicines for treating atherosclerosis were not studied in detail. Therefore, the present review aimed to highlight the molecular mechanism of different types of herbs or alternative medicines for the treatment of atherosclerosis in general population.

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is the disease which causes thickening of the arterial wall and loss of elasticity in it. The risk factors for the disease include hypertension, hyperlipidemia, type 2 diabetes mellitus, smoking and modern lifestyle (Rafieian-Kopaei et al. 2014; Chen et al. 2013). These factors disturb the oxidant and antioxidant balance which results in overproduction of reactive oxygen species (ROS). The increase in ROS and decrease in superoxide dismutase (SOD) was related with the endothelial abnormality (Mittal et al. 2014; Yu et al. 2013). It is noteworthy that the ROS production is inversely related to the nitric oxide (NO) levels. NO was described to be one of the most vital signaling molecules generated by the endothelium (Khan et al. 2015). Since NO is important in vasodilation, if there is a decrease in NO production, it leads to deteriorate endothelial function and arterial wall architecture (Khan et al. 2015). In addition, the main principle of flow-mediated dilation is to decrease the superoxide-mediated NO breakdown and develop the bioactivity of the endothelium-derived vasodilator NO by increasing NO synthesis (Grassi et al. 2013).

Once, the NO production is depleted, the levels of LDL increases gradually (Figure 1). In the presence of underlying risk factors like hypertension results in injury to the endothelial cells and causes infiltration of LDL in the tunica intima. Then, the LDL is converted to minimally modified (mmLDL) in which LDL is still

be recognized by the LDL receptors. The monocytes are then, attached to endothelial cells via mmLDL. Furthermore, mmLDL undergoes oxidation, which leads to formation of oxidized LDL (Anna et al. 2013). Then, the inflammatory process gradually takes place. It starts with activation of immune cells such as macrophages and T cells followed by lipid rich foam cells. Foam cells penetrate and accumulate on the vessel wall and gradually become toxic due to the oxidation (Veazie et al. 2005; Pearson et al. 2002).

During the inflammatory response, a study reported that there was initiation of protein kinase C (PKC) and the production of the granulocyte/macrophage colony-stimulating factor (GM-CSF) prompted the macrophage proliferation (Veazie et al. 2005). A study mentioned that when the macrophages reacted with oxidized-LDL, there was release of macrophage inhibition factor (MIF) by cytokine or interleukin- γ (Wen-Harn et al. 1995). MIF is recognized as an inhibitor of the random migration of macrophages (Pearson et al. 2002; Smith et al. 2006). Along with MIF, selectins are also involved in initial leukocyte recruitment as an adhesion molecule (Ross 1999; Khan et al. 2015).

The effusion of leukocytes into intima of arterial wall occurs in several phases. At first, the leukocytes are seen to be undulating along the endothelium which comprises calcium dependent low-affinity adhesion molecules such as E-selectin (endothelium), L-selectin (leukocytes) and P-selectin (platelets and endothelium) (Grassi

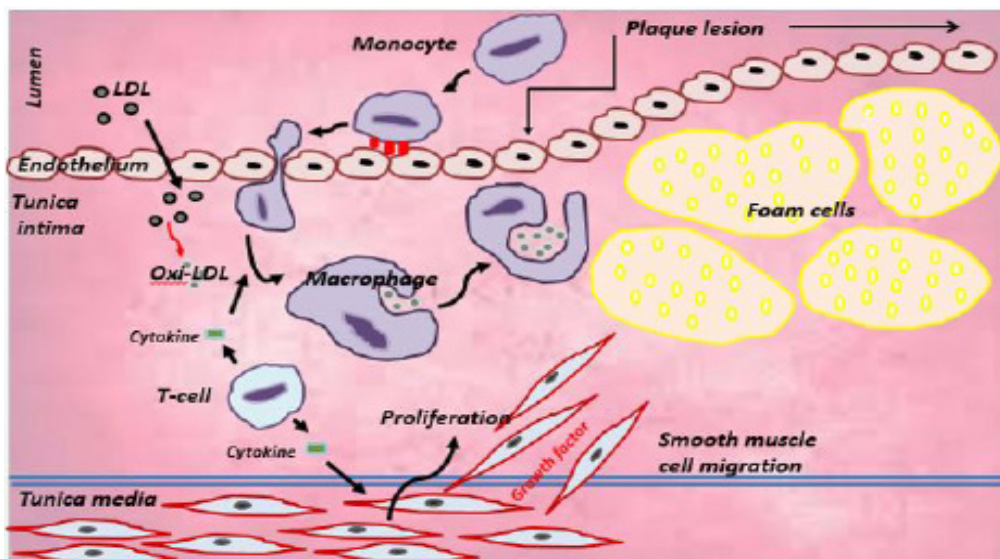


Figure 1: Pathophysiology of atherosclerosis in the human coronary artery endothelial cells.

et al. 2013). Secondly, it implicates a stable bond and then migrates into the intimal of artery along with vascular adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) (Rakesh et al. 2005). Studies on immunohistochemistry showed increased P-selectin protein expression in the endothelium plaques of patients with unstable angina (Bauriedel et al. 1999; Senokuchi 2004). Hence, P-selectin has an important role in atherosclerotic lesions. Prior research studies also observed the increase ICAM-1, VCAM-1, and E-selectin expression in the aortas of apoE_{-/-} mice and proved the significant link between the adhesion molecules and the disease (David 1996; Kathryn & Moore 2013).

MATERIALS AND METHODS

Pubmed, Science Direct, Scopus, ISI Web of Knowledge and Google

scholar were searched using the terms 'atherosclerosis', 'alternative medicines', 'herbs', 'atherosclerotic pathway'.

HERBS USED IN THE TREATMENT OF ATHEROSCLEROSIS

GARLIC (*Allium sativum*)

Allium sativum or garlic, belongs to the *Allium* family, is the highly consumable food worldwide. It is used as the general ingredient in cooking due to its sturdy aroma and pleasant taste. Traditionally, garlic has been used to boost up the immune system during fever, common cold or flu, hypertension, menstrual problems and cough (Pan et al. 2004). The beneficial effect of garlic is probably due to the presence of major bioactive compound, alliin (allyl 2-propenethiosulfinate or diallyl

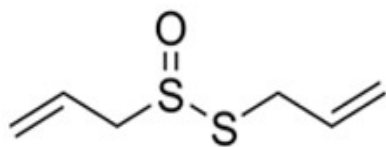


Figure 2: Chemical structure of Allicin (Wallock-Richards et al. 2014)

thiosulfinate). Allicin ($C_6H_{10}OS_2$) (Figure 2) is shown to possess the positive effect against atherosclerosis (Bayan et al. 2014). The ingestion of large amounts of fresh garlic (0.25 to 1.0 g/kg) has been shown to improve the atherosclerotic status (Chan et al. 2013). This can be proven by a study on rats where at 28 days of feeding the hypercholesterolemic rats with 400 g/kg garlic extract, showed lower concentration of serum low-density lipoprotein cholesterol (LDL-C) cholesterol and higher HDL-C cholesterol ($P < 0.05$). Therefore, garlic extract has protective effects on HDL in rats where garlic extract attenuated LDL levels and improved HDL levels (Ebrahimi et al. 2015)

POMEGRANATE (*Punica granatum*)

Pomegranate (*Punica granatum*) is the pre-historic fruit and commonly known as the fruit of Eden (Al-Quran) due to its delightful palate and significant healthiness effects. In ancient time, this fruit was only available in the Himalayas, Northern India to Iran. Currently, it is available worldwide as it has been cultivated and naturalized all over the world. Pomegranate is used as the traditional medicine to heal ulcers, relief diarrhea, intestinal worms and cough and also improve the infertility (Zarfeshany et al. 2014; Akhtar et al. 2015). The juice of pomegranate along with its peel contains antioxidants like anthocyanin and ellagitannin (Figure 3B), gallic acids, punicalagin (Figure 3A), and quercetin (Fischer et al. 2011). In the cultured human endothelial cells and hypercholesterolemic mice, the activation of ELK1 and pCREB (oxidationsensitive responsive genes) was reduced. Meanwhile for the endothelial nitric oxide synthase, the expression was elevated by the action of pomegranate juice and fruit extract. This study by Gupta et al. at pre-treatment at 200 mg/kg for 21 days showed that the reduction of oxidative stress, increase in eNOS

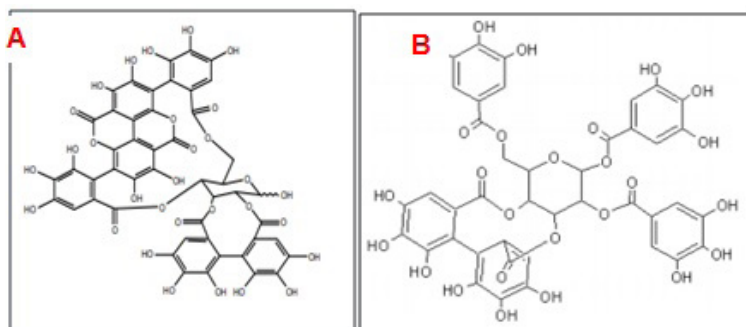


Figure 3: (A). Chemical structure of Punicalagin, ($C_{48}H_{28}O_{30}$) (Moneim, 2015) and (B). Monomeric Ellagitannin Nupharin ($C_{44}H_{32}O_{27}$) (Lipińska et al. 2014)

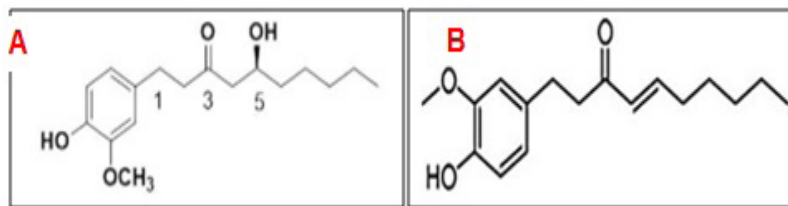


Figure 4: (A) Chemical structure of (S)-[6]-Gingerol (Kim et al. 2015) and (B) [6]-Shogaol (Peng et al. 2015)

expression, inhibition of apoptosis and atherogenesis was mainly caused by the polyphenolic antioxidant compounds found in the pomegranate juice (Gupta et al. 2015).

GINGER (*Zingiber officinale*)

Ginger (*Zingiber officinale*) is a universally consumed spice and used in the traditional medicine for treating respiratory, gynaecological, gastrointestinal and inflammatory sicknesses (Pakrashi et al. 1975). The bioactive compound of ginger, (S)-[6]-Gingerol ($C_{17}H_{26}O_4$) (Figure 4A), holds anti-angiogenic, anti-metastatic, anti-platelet and anti-hyperlipidaemic activities (Nammi et al. 2010). Moreover, (S)-[6]-Gingerol is recommended to have an anti-atherosclerotic effect as it inhibits biglycan production, which is an initial lipid binding mediator in atherosclerosis (Kamato et al. 2013). Furthermore, [6]-Shogaol ($C_{17}H_{24}O_3$) (Figure 4B), another active compound found in ginger most active compound at 2.7 μM of concentration able to constrain PDFG-BB-stimulated propagation in vascular smooth muscle cells (VSMCs) by hindering the cell-cycle conversion at G2/M phase (Liu et al. 2015). According to Bhandari

et al. 1998, the ethanolic extract of ginger at 200 mg/kg was able to lessen atherogenesis and decrease LDL levels in cholesterol-fed rabbits (Bhandari et al. 1998).

CINNAMON (*Cinnamomum spp.*)

Cinnamon, (*Cinnamomum crassinervium*), is one of common remedy all over Asia, Africa and Europe. Consumption of cinnamon bark is believed to relieve cold, diarrhoea, queasiness and pain. Cinnamon and its active compounds mainly eugenol exhibit anti-diabetic, anti-oxidant, anti-microbial, anti-cancer and anti-inflammatory properties (Lee et al. 2003; Kim et al. 2006; Kwon et al. 2010). Cinnamon water extract (CWE) also moderates the LPS-induced inflammatory markers including tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) in *in vivo* subjects. The anti-inflammatory actions of cinnamon are mainly caused by the inhibition of both I κ B α degradation and MAPK initiation (Matan et al. 2006). Regarding the anti-atherosclerotic effects, cinnamon displays effective hypotensive, hypolipidaemic, and vasodilatory actions (Jin et al. 2011; Hong et al. 2012; Nyadjeu et al. 2013). Interestingly, Kwon et al. 2015 has

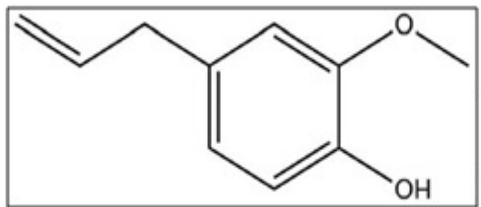


Figure 5: Chemical structure of Eugenol (Faye et al. 2017)

proved that the cinnamon extract at 40 mM able to suppresses the PDGF-BB-induced proliferation of VSMCs through moderating the expression of p21 and p27, two cell cycle regulatory proteins (Kwon et al. 2015). According to a study, eugenol ($C_{10}H_{12}O_2$) (Figure 5), the active compound present in cinnamon, suppresses the monocyte differentiation and macrophage scavenging activity in human monocytic cells (Raffai et al. 2014). Eugenol ameliorates high blood pressure by enhancing the NO production in induced hypersensitive rats at 20 mg/kg (Nyadjeu et al. 2013). Besides, CWE (500 g/kg) also reduces hyperlipidaemia as well as inhibits LDL phagocytosis, protein-glycation, and atherosclerosis (Hong et al. 2012).

GREEN TEA (*Camellia sinenses*)

Green tea or *Camellia sinenses* is one of the most universally consumed beverages. The health benefits for about 36% of dried green tea of green tea are recognized for its high polyphenolic contents (Balentine et al. 1997). The main polyphenols in green tea are catechins, which elicits anti-tumorigenic, anti-carcinogenic, anti-mutagenic anti-inflammatory and anti-diabetic effects (Valcic et

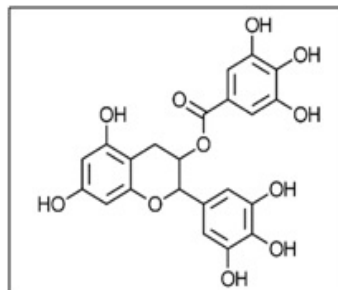


Figure 6: Chemical structure of EGCG (Chen et al. 2015)

al. 1996; Isozaki et al. 2001; Rizvi et al. 2001; Yang et al. 2013). The main catechin, epigallocatechin-3-gallate (EGCG) ($C_{22}H_{18}O_{11}$) (Figure 6) has been considered as an anti-atherosclerotic agent in green tea. A study by Orozco-Sevilla et al. 2013, intraperitoneal 1 mg/kg injection of EGCG diminishes the intimal hyperplasia in the wounded carotid artery model (Orozco-Sevilla et al. 2013). In addition, EGCG prevents serum-, Ang II-, PDGF-BB-, TNF- α -, and high glucose-induced proliferation of VSMCs (Lee et al. 2013; Lin et al. 2014). According to many researchers, EGCG showed reduction of Ang II- and IL-6-induced production of C-reactive protein and ROS in VSMCs (Li et al. 2012), inhibited the immigration and invasion of VSMCs (Tachjian et al. 2010) and also suppressed the TNF- α -induced expression of VCAM-1 and adhesion of macrophages to endothelial cells (Ludwig et al. 2004).

PALM OIL

The palm tree, (*Elais guineensis*) is a pre-historic tropical plant which is originate in West African countries. Traditionally, the oil is used in cooking and making dairy products such as

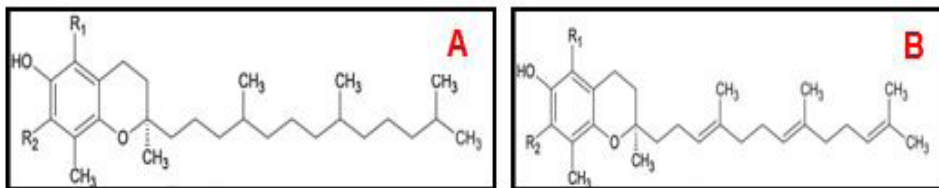


Figure 7: Chemical structure of Tocopherols (A) Tocotrienols (B) (Saini & Keum, 2016)

sweets, margarine, cereals etc. Large scale palm crops are found across the tropical regions including Malaysia and Indonesia which are the leading countries producing palm oil (PO), approximately more than 80% of global production (Sundram et al. 2003; Mukherjee & Mitra 2009). Palm oil has the high level of vitamin E which contains complex elements such as tocopherols and tocotrienols (Colombo 2010). These natural antioxidants like tocopherol ($C_{29}H_{50}O_2$) (Figure 7A) and tocotrienol ($C_{29}H_{44}O_2$) (Figure 7B), act as free radical scavengers and are believed to show a defensive role in cellular aging, atherosclerosis, arthritis, cancer and Alzheimer's disease (Kinsella et al. 1993). Studies proved that the supplementation of PO in the diet regulates plaque formation in the arteries and improves the atherosclerosis (Kinsella et al. 1993; Sambanthamurthi et al. 2011; Sambanthamurthi et al. 2011). *Ex vivo* also reported that PO regulates the copper-mediated oxidation of endothelial cells and promotes vascular lessening in aortic vascular beds contracted with noradrenaline (Sambanthamurthi et al. 2011.).

COCONUT OIL

Coconut, also known as *Cocos*

nucifera (DebMandal et al. 2011), a natural product acknowledged for its several nutritional and medicinal properties has gained attention in the modern medical society. Coconut oil is derived from the dehydrated kernel or meat of coconut, also known as copra (Nevin & Rajamohan 2004). It possesses 90-95% saturated fatty acids and is frequently used as a tropical edible oil in Asian countries (Eyes et al. 2016). The most abundant fatty acid in coconut oil is lauric acid ($C_{12}H_{24}O_2$) (Figure 8) which has antiviral, antifungal, and antibacterial properties (Creswell & Brooks 1971; Feranil et al. 2011). Several therapeutic studies were conducted on coconut oil against atherosclerosis and cardiovascular disease (Nevin & Rajamohan 2004; Intahphuak et al. 2010; Shankar et al. 2013). The consumption of coconut oil in daily food reduces the risk of heart disease compared to other dietary oils. It reduces the cholesterol level, lower the body fat deposition, improves free radicals scavenging activity, increase the antioxidant levels, and decreases the incidence of cardiac disease (Nevin & Rajamohan 2004; Nevin & Rajamohan 2008; Marina et al. 2009). An *in vitro* and *in vivo* study by Ibrahim et al. 2017 which focused on wound healing process proved that for *in vitro*, coconut oil in concentration of

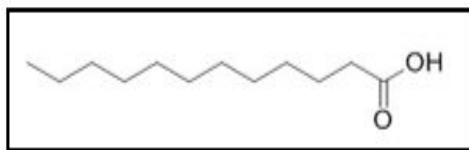


Figure 8: Chemical structure Lauric acid (Dayrit, 2015)

6 and 12 g/mL significantly enhanced the proliferation of human umbilical vein endothelial (HUVEC), fibroblast (CCD-18) and retinal ganglion (RGC-5) cells, and also enhanced the phospho-VEGFR2 expression in HUVECs. For *in vivo* study, coconut oil at 25, 50 and 100 g/mL significantly stimulated the *ex vivo* blood vessel development. Injured rats treated with coconut oil had significantly minor wound size, higher wound curative percentage, and smaller wound closure period, signifying that ingestion of coconut oil remarkably endorsed the wound healing process (Ibrahim et al. 2017).

OLIVE OIL

Olive is the fruit of *Olea europaea*, from family Oleaceae, a tree originated in Mediterranean Basin. Olive oil is traditionally used as the home-made skincare, cleanser, and moisturizer (Widmer et al. 2013; Dimitirou et al.

2016; Covas et al. 2015). Olive oil intake is related with the risk of coronary artery disease as it contains major phenolic compounds, oleuropein ($C_{25}H_{32}O_{13}$) (Figure 9A) and hydroxytyrosol ($C_8H_{10}O_3$) (Figure 9B) (Dimitirou et al. 2016). These phenolic compounds reduce hypercholesterolemia by decreasing the plasma LDL and total cholesterol levels, increasing the high-density lipoproteins (HDL) level and the activity of antioxidant enzymes in rats fed with a cholesterol-rich diet. It was explained that the olive oil exerts its anti-atherogenic effect by suppressing the ERK1/2 initiation, blocking the G1 to S cell cycle which in turn inhibits the vascular smooth muscle cells (VSMCs) proliferation (Abe et al. 2012). Additionally, olive oil inhibits the neutrophil activity and protects the endothelium in the arterial wall (Czerwinska et al. 2014).

OMEGA-3

Omega-3 is a polyunsaturated fatty acids contain of eicosapentaenoic acid ($C_{20}H_{30}O_2$) (EPA) (Figure 10A), docosahexaenoic acid ($C_{22}H_{32}O_2$) (DHA) (Figure 10B) and α -linolenic acid (ALA). The main components for omega-3 are EPA and DHA (Zheng et al. 2013). Over the years, omega-3

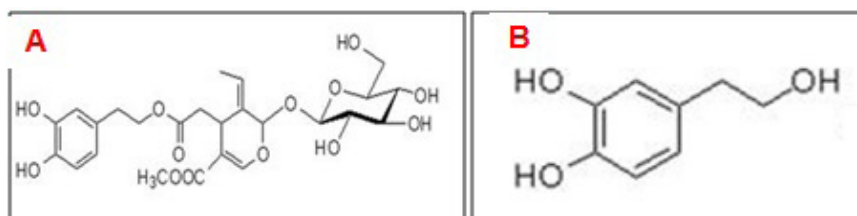


Figure 9: Chemical structure of Oleuropein (A) and Hydroxytyrosol (B) (Bulotta et al. 2014)

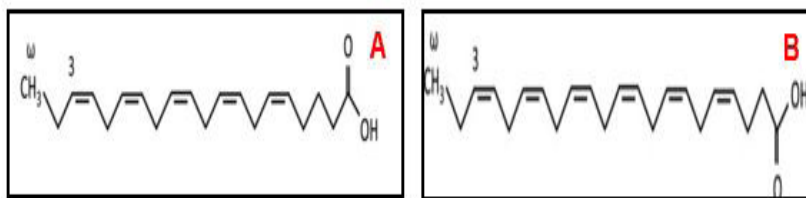


Figure 10: Chemical structure of Eicosapentaenoic acid (EPA) (A) and Docosahexaenoic acid (DHA) (B) (Shaikh et al. 2015).

FFA, particularly DHA, has been widely studied as it improves the breast cancer by suppressing the cell proliferation and promoting the cell apoptosis (Van der Burg et al. 1988; Manna et al. 2008). The consumption of omega-3 and eicosapentaenoic acid (EPA) is contrariwise linked to the risk of development of coronary artery and cerebrovascular diseases. Therefore, the researchers acclaimed the high intake of fish oil and omega-3 to improve the cardiovascular health (Kris-Etherton et al. 2002; Wang et al. 2006). Moreover, DHA is proven to alter the transferring of leukocytes during inflammatory process and validate that this includes disturbance of intracellular transport mechanisms used to present adhesion molecules on the surface of cytokine-stimulated endothelial cell (EC) (Yates et al. 2011). DHA also inhibits the development of non-small lung tumors through an ROS-mediated inactivation of the PI3K/Akt signaling pathway (Yin et al. 2017). A study on human umbilical vein endothelial cells (HUVECs) by using α -linolenic acid (ALA) treated with high concentration of 100 ng/mL, significantly reduced LPS-induced release of soluble intercellular cell adhesion molecule-1 sICAM-1 and soluble vascular cell adhesion

molecule 1 sVCAM-1, without effect on THP-1 adhesion. In addition, there was no radical scavenging activity observed (Shen et al. 2018).

PHYTOESTROGEN

Phytoestrogens (PEs) are naturally occurring plant that is normally produced in large range. It mimics or modulates endogenous hormones like oestradiol by exerting the oestrogenic or/and anti-oestrogenic effects (Setchell et al. 2001). It is usually present in vegetables, fruits and whole grains. It is also found abundantly in medicinal plant, belongs to the *Leguminosae* family (Dixon 2004; Michel et al. 2013), in soy/soy protein, kudzu, red clover, licorice, rhubarb, hops, chasteberry and yam (Hajirahimkhan et al. 2013). PEs are divided into three main classes: isoflavones (genistein, daidzein, biochanin A, formonetin, and equol); lignans (enterolactone, enterodiol, secoisolariciresinol, pinoresinol, matairesinol, lariciresinol); and coumestans like coumestrol (Cornwell et al. 2004; Ibarreta et al. 2010). Isoflavones originate in legumes-mostly in soybeans, flaxseed (a major source of lignans), and for coumestans, present in clover, alfalfa and soybean sprouts (Cassidy 2003).

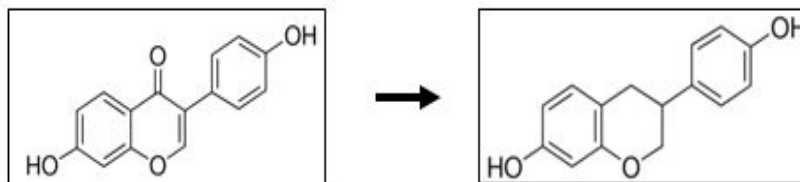


Figure 11: Structural formula of Daidzein oxidised into Equol (Sirotkin & Harrath, 2014).

It was mentioned that isoflavones are the main active compounds in soy/soy protein which exerts multiple therapeutic effects against adverse outcomes in human health (Chen et al. 2003).

Depends on the countries and their cultures, the intake of isoflavones varies. In Asian population, approximately 20-50 mg of isoflavones are used daily (Mense et al. 2008; Fritz et al. 2013). There are epidemiological studies which suggested the recommended dose of isoflavones in reducing the risk of cardiovascular disease in postmenopausal women (Moreira et al. 2014). However, the mechanism of action of phytoestrogens or isoflavones against atherosclerosis is still under debate. It is noteworthy that PE serves as oestrogen antagonist by blocking the potent endogenous oestrogen to bind its own receptor. Several literatures provide conflicting interest of PEs against its mechanism of action (Younes & Honma 2011; Rietjens et al, 2013; Paterni et al. 2014). The intricacy of PE is found at its cellular and molecular level. Many studies highlighted that the effect of PE depends on its dose, class, presence or absence of endogenous oestrogens and its receptor oestrogen receptors (ER and ER β) (Benassayag et al. 2002).

Although, there are several studies

observed the positive effect of herbs or compounds against atherosclerosis, the role of phytoestrogens or isoflavones in regulating the disease was not summarised, to date. In this review, we focused mainly on the mechanism of isoflavones such as genistein, daidzein and equol in improving the vascular health. We also emphasised on which isoflavones provide better therapeutic effect in reducing the plaque lesion, thickness of arterial wall, levels of LDL and increasing the HDL levels in the blood circulation. The effect of these three bioactive compounds on atherosclerosis were further discussed in this review.

DAIDZEIN (C₁₅H₁₀O₄)

Daidzein (4', 7-dihydroxyisoflavone) (Figure 11A) is a natural isoflavones which belongs to the non-steroidal oestrogens (Cassidy 2003). It is generally derived from the leguminous plants like soy and mung bean. It is the second most abundant isoflavones in soy following genistein. Asians typically consume 15-50 mg of daidzein per day, compared to the Western who consume approximately 1-2 mg (Froyen et al. 2009). Interestingly, in countries like Japan where soy consumption is high, there is about 85% lower rate of health problem than in the West. It is

also the major bioactive component in traditional Chinese medicine, Gegen (Wang et al. 2003) which is used frequently in the treatment of fever, diarrhea, liver injury, diabetes, acute dysentery, cardiac dysfunctions (Wong et al. 2011).

The chemical structure of daidzein is alike to mammalian oestrogen and it applies dual-directional function by substituting/meddling with oestrogen and the oestrogen-receptor (ER) complex. Consequently, daidzein has protective role alongside some diseases which are connected to the regulation of oestrogen such as cardiovascular diseases, osteoporosis, diabetes and also breast cancer (Vitale et al. 2013). Interestingly, daidzein has a sum of other biological activities independent of the ER such as anti-inflammatory, protection of skin and the nerves and inhibition of oxidative damage. These advantageous effects are essentially due to regulation of the immune response (Masilamani et al. 2012), rummaging of oxygen free radicals, suppression of proliferation and many more. Nevertheless, when daidzein is existing in the bound form "daidzin", it becomes inactive.

Some metabolites of daidzein show a similar pattern. Equol ($C_{15}H_{14}O_3$) (Figure 11B) is a metabolite of daidzein which commonly present in the soy/soy protein (Törmälä et al. 2008). Soy isoflavones able to biotransform into potent oestrogenic metabolite, equol, enhancing its actions. Equol possesses greater affinity for oestrogen receptors, unique anti-androgenic properties, and superior antioxidant activity (Kang et al. 2007). Equol is metabolized from

daidzein in the body with the help of intestinal flora. This compound increases the bone mineral density, affect the vasomotor symptoms, decreases the levels of LDL and improves the endothelial dysfunction (Sirtori 2001; Cassidy et al. 2006).

In a study using hypercholesterolaemic model observed that treatment with daidzein for 6 months significantly reduced the triglyceride (TG) concentration along with ESR- β Rsa1 genotype but not the other cholesterol marker which is LDL. Daidzein was found to down-regulate the uric acid level, an important factor for atherosclerosis (Qin et al. 2014). In animal model of orchidectomized (Orx) rats, subcutaneous high doses injection of genistein and daidzein showed decrease in serum cholesterol levels compared to the ovary intact (IA) group (Sosi-Jurjevi et al. 2007). Increased nitric formation and damage to endothelium integrity are alleviated with supplementation of daidzeins (0.2 mg/kg per day, 0.4 mg/kg per day and 0.8 mg/kg per day). Daidzein exerts oestrogen-like effect on endothelium and inhibits caveolin-1 expression which in turns increase in nitric oxide bioavailability and eventually improves the endothelium dysfunction (Sharma et al. 2012). Another study in streptozotocin-induced diabetic rats also demonstrated that chronic supplementation with daidzein ameliorated endothelial dysfunction. According of Roghani et al. 2013, daidzein significantly enhanced the vascular contractile-relaxation response activity via NO and prostaglandin-dependent

pathways and it also inhibited lipid peroxidation. Daidzein as well as equol were also conveyed to show a significant effect on hypertension by regulating vascular smooth muscle tone thru adapting a stability between vasodilator and vasoconstrictor, modulation of humoral systems and renal function. Martin et al. 2008 stated that, currently, anti-hypertension effect of daidzein has merely been established in animal models, and it still needs further justification in human medical trials. Other studies also identified that daidzein related to catecholamine synthesis and secretion which contributed in decreasing the risks of atherosclerosis (Liu et al. 2007; Yanagihara et al. 2014). A study was conducted where rat with ischemia/reperfusion were given pre-treatment using daidzein, showed significantly reduced myocardial damage induced by ischemia reperfusion. Thus, it was concluded that daidzein improved myocardial contractile dysfunction, inhibition of myocardial apoptosis and lessened myocardial infarct size via activation of NF- κ B pathway. This NF- κ B pathway regulated the expression of inflammatory cytokines via its antioxidant activity (Kim et al. 2009; Gil-Izquierdo et al. 2012; Gencel et al. 2012). In conclusion, daidzein reveals protective role against atherosclerosis and cardiovascular disease.

GENISTEIN (C₁₅H₁₀O₅)

Genistein (40,5,7-trihydroxyisoflavone) (Figure 12), a natural flavonoid of *Leguminosae* plants, is a phytoestrogen which possesses both

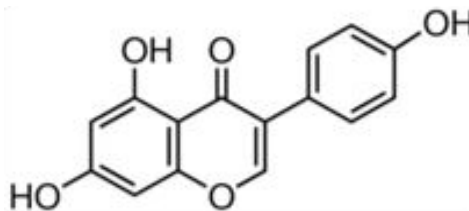


Figure 12: Structural formula of Genistein (Sirotkin & Harrath, 2014)

agonist and antagonist oestrogenic property. With the presence of several pharmacological compounds, genistein become a potential agent for the deterrence and treatment of chronic diseases. Genistein acts as a vasodilator, anti-thrombotic and anti-atherosclerotic agent, through different mechanisms of action (Williamson-Hughes et al. 2006; Messina et al. 2006; Lee 2006). Genistein also has structural similarities with tamoxifen, a chemopreventive agent, and with equol, a dietary isoflavone formed by gastrointestinal flora (Kwon 2014). Besides the oestrogenic activities of genistein, it also contributes anti-oestrogenic activities by competitively binding to the same receptors as oestradiol (Kwon 2014). Over the years, genistein was found to improve the atherosclerosis is several ways. Genisteinindoseof0.1 mol/L improved endothelial nitric oxidase synthase (eNOS) uncoupling concerned with sirtuin-1 pathway in ox-LDL-induced human umbilical vein endothelial cells (HUVECs). It was mentioned that eNOS uncoupling is a major key factor which causes endothelial dysfunction in atherosclerosis (Zhang et al. 2016). Moreover, it was found to decrease the superoxide production and NOX4 expression, increase the

ratio of BH₄/BH, the expression of GTP cyclohydrolase 1 (GCH1) and dihydrofolate reductase (DHFR) (Babu et al. 2013).

It was observed that genistein blocks the diabetes-induced endothelial dysfunction. The suppression of linkage of the monocytes adhesion in the endothelial cells, inhibition of endothelial production of monocyte chemoattractant protein-1 (MCP-1) and interleukin 8 (IL-8) was observed following genistein supplement (1g/kg) for 8 weeks in experimental female Sprague–Dawley rats. Genistein reduced the monocytes and adhesion molecules secretion via cAMP/PKA pathway (Xiang et al. 2012). Another study also revealed that genistein inhibits angiotensin II-induced production of VSMCs and stimulates the endothelial cells production (Yi et al. 2011). Molecular study using HUVECs observed that the treatment with genistein decreases inflammatory response via initiation of nuclear factor erythroid 2-related factor (Nrf2)/ heme oxygenase-1 (HO-1) pathway (Chen et al. 2011). Genistein significantly decreased the oxidised-LDL level by stimulating the macrophage/ monocyte chemoattractant protein-1 (MCP-1) expression, and inhibiting the vascular cellular adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1) expressions (Zhang et al. 2013). Overall, genistein proved to have beneficial role in reverting atherosclerosis and related cardiovascular disease.

Genistein consumption was also found to avert the increases of iNOS activity in diabetic wound tissues in

a dose-dependent manner (Tie et al. 2013) On the contrary, a previous study showed that genistein and daidzein activate eNOS and enhance NO production through the estrogen receptor (ER) pathway in RAW 264.7 macrophages (Nakaya et al. 2005). In light of these experimental data, isoflavones act to maintain the production of NO in normal physiological conditions, but prevent the overproduction of NO through inhibiting the expression and activity of eNOS in a pathological state.

CONCLUSION

Commonly consumed natural products such as garlic, ginger, cinnamon, green tea, etc showed significant positive effect on vascular health. Herbs or natural products are considered to be a widely consumed as dietary food. We summarized the findings from previous literature highlighting the possible mechanism of each herbs/ alternative medicine in reverting the atherosclerotic changes. Herbs improve endothelial nitric oxidase synthase (eNOS), increase nitric oxide formation, reduce serum cholesterol levels, reduce inflammatory response, inhibit angiotensin II-induced production of VSMCs and stimulate the endothelial cells production nuclear factor erythroid 2-related factor (Nrf2)/ heme oxygenase-1 (HO-1) pathway or activation of NF-κB pathway. Further experimental studies and clinical trials on the comparison between the anti-atherosclerotic roles of the different alternative medicines are essential in future. At the present juncture, it is

uncertain to recommend the specific dose of alternative agents in prevention or treating atherosclerosis. The results from the clinical trials would help in identifying the specific dose of different alternative agents in reducing the risk of atherosclerosis.

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