REVIEW OF LITERATURE
Chapter – I

Ziziphus Jujuba Mill.
II. REVIEW OF LITERATURE

CHAPTER I

*Ziziphus jujuba Mill.*

1. Introduction

Traditional medicines are used by near about 80 per cent of the world's population. Medicinal plants contain inherent active ingredients used to cure diseases or relieve pain [53]. These are not only used for primary health care in rural areas but also in developing countries. In developed countries modern medicines are predominantly used. While the traditional medicines are derived from medicinal plants, minerals, and organic matter, the herbal drugs are prepared from medicinal plants only [54].

Jujubas are species of the genus *Ziziphus* Tourn. ex L. *Ziziphus* belongs to the family Rhamnaceae. The name *Ziziphus* is related to an Arabic word used along the North African coast, zizoufo used for *Z. lotus* (L.) Desf., but also related to the ancient Persian words zizfum or zizafun and ancient Greeks used the word ziziphon for the jujuba. There are two major domesticated jujubas, *Ziziphus mauritiana* Lam. the Indian jujuba or ber, and *Ziziphus jujuba Mill.* the Chinese or common jujuba. The Chinese jujuba has been introduced into more than 30 countries and is becoming increasingly popular for its wide adaptations, easy management, early bearing, rich nutrition and multiple uses [55]. Figures 1-3 show the different stages of jujuba ripening.
FiG. 1 Unripe fruit of *Ziziphus jujuba Mill.*

FiG. 2 Ripe fruit of *Ziziphus jujuba Mill.*

FiG. 3 Semi-dry and ripe fruit of *Ziziphus jujuba Mill.*
Chinese jujuba is a well-known oriental medicinal plant that has various biological activities. *Ziziphus jujuba Mill.* is indigenous and naturalized throughout many Asian and African countries specially with a history over four thousand years in China [56-57]. It has been widely planted in re-forested areas within the Yellow River valley in China, and chosen as a variety compatible with the present ecology and economy [58]. Currently, the *Ziziphus jujuba* tree can be found around the globe [59].

*Ziziphus jujuba Mill.* is a thorny plant, and more than 700 cultivars have been found in China, especially in Henan, Shandong, Hebei, Shanxi, Shaanxi, Ningxia, Xinjiang, and Gansu provinces. In Flora Iranica 5 species were listed for Iranian Plateau namely *Z.* spina-christi, *Z.* nummulatoria, *Z.* jujuba, *Z.* mauritiana and *Z.* oxyphylla [60]. Because of its broad pharmacological effects, it has been used for thousands of years in traditional Chinese medicinal prescriptions [58-59]. The fresh *Ziziphus jujuba* fruit is highly desired by many cultures and available in Korean, Chinese, Iran, Vietnamese, and Indian stores. The Chinese share of world jujuba production is about 90% and its production has recently increased due to the demands for food and pharmaceutical applications [61-62]. Chinese jujuba is a kind of favorable and profitable fruit, and is much admired for its high nutritional value. It is customarily employed as a crude drug for analeptic, antibechic and palliative purpose, and also used as food, food additive and flavor. The fruits are claimed to purify the blood and aid digestion. Nearly every part of *Ziziphus* plants can be utilized. The roots are used in fever and to cure wounds and ulcers. The bark is used as a remedy in diarrhoea [57]. Jujuba dried fruit called Dazao in China which has been used as a traditional Chinese medicine (TCM) for immunity stimulant, antitumor activities, etc.[50, 63-64]. As for the chemical constituents of this plant, several triterpenoid acids, cyclopeptide alkaloids, saponins, and flavonoids have been isolated from its fruit, bark and leaf [64-69].
2. The Major Cultivated Species

2.1 Indian jujuba (*Ziziphus mauritianana* Lam.)

**Synonyms**


The species has a wide range of morphologies from shrubs to small or medium sized trees which might be erect, semi-erect or spreading. Height can vary from 3-4 to 10-16 m or more although trees of 20 m are rare. Fruit is a glabrous globose or oval edible drupe varying greatly in size from 1.5 cm diameter but some oval varieties can reach 5 x 3 cm. The pulp is acidic and sweet, the fruit greenish, yellow or sometimes reddish.

2.2 Chinese jujuba (*Ziziphus jujuba* Mill.)

**Synonyms**


Shrubs or small trees up to 8-10 m high with rigid spreading boughs and stiff branches; an appearance often producing a gnarled shape. Fruit is an ovoid-oblong edible drupe 1.5-2.3 cm long, dark reddish brown to black, each being short stalked and may be pendulous. Pulp is sour to sweet. Chinese jujuba is native to temperate Asia, particularly China and neighbouring areas of Mongolia and the Central Asian Republics. It is mostly cultivated in China, India, Iran, Central Asia and southwest Asia.

Ber seeds are enclosed within a hard woody endocarp known as the stone which is sometimes wrongly referred to as the seed. Each fruit contains one stone embedded in the pulp at the centre of the fruit. The stone can be depulped in many ways: manually by removing the pulp, pounding dried fruits in a mortar, or by running the fruits through a macerator with water and floating off the pulp. Stones
vary in shape from round to subovate to ovate with more or less pronounced ridges on the outer surface [70].

3. **The Minor Cultivated Species**

There are two species of *Ziziphus* which are still cultivated on a small scale. They are described below.

3.1 **Ziziphus spina-christi (L.) Desf.**

*Synonyms*


*Ziziphus spina-christi* is a species of the Middle East through Arabia and West Africa to N. E. Africa, Ethiopia and Eastern Africa, especially the drier tropical areas. It is wild in the Middle East, especially Iran, Saudi Arabia and also farther west in Turkey.

3.2 **Ziziphus lotus (L.) Lam.**

*Synonyms*


This species is a spiny shrub growing up to 1.5 m tall and resembling *Z. jujuba*. However, fruiting branchlets are not deciduous and twigs are grey.

4. **Vernacular Name of Jujubas**

Vernacular names frequently refer only to a jujuba fruit. The names used in different regions, countries and languages, with reference to English, Chinese, Indian and Iranian jujubas are following:

English: Jujuba; Indian jujuba, Indian plum, Indian cherry, Indian date; Chinese jujuba; Chinese date; Chinese fig; Cottony jujuba
China: Hong tsao, Lang tsao, Ta tsao, Tsao tse

India: Rajabadari (Sanskrit); Beri (Punjabi); Kul (Bengali); Bogori (Assamese); Bodori (Uriya); Ber, Bor, Bordi, Boyed (Gujarati); Ber (Hindi); Bor (Marathi); Badaram, (Malayalam); Yolachi, Bogari (Kannada); Vadari (Tamil); Renu (Telugu); Ber (Urdu); Jangri (Sindhi) [54, 71-72].

Iran: Annab, Onnab, Kanar, Kunar, Nabik [10, 71-72]

5. Biochemical Composition

Chinese Ziziphus jujuba fruits are rich in various essential nutrients with carbohydrates contributing in largest portion (55–85%), followed by moisture (25–30%), crude fiber (2.4–8.4%), crude protein (2.9–6.6%), crude fat (0.4–1.0%), and several other essential vitamins and minerals [50]. Species of Ziziphus are considered to be multipurpose plants although use of the fruits is the major focus of interest. Chinese jujuba is significant source of polysaccharides, minerals such as iron, phosphorus and calcium (Ming and Sun, 1986), Vitamin C, B complex and P [73-74]. From the different species of the genus Ziziphus, peptide and cyclopeptide alkaloids, flavonoids, sterols, tannins, betulinic acid and triterpenoidal saponin glycosides have been isolated and chemically identified [57, 75-82]. Different parts of the plant have medicinal value due to their constituents. Z. jujuba fruits have been shown to be responsible for various biological activities including antiproliferation of cancer cell [83], regulation of immune function [84] and reduction of blood triglyceride [85].

This section looks in particular at the nutritive composition of fruits.

**Vitamins:** Ziziphus jujuba fruits are good source in vitamins C, B1 (thiamine) and B2 (riboflavin) [73-74, 86-87]. It has also known to have a high Vitamin P content. Vitamin P (bioflavonoids) enhances the action of Vitamin C. Ascorbic acid and Vitamin P act together to help maintain the thin walls of capillaries. Vitamin P also has anticancer, antibacterial, anti inflammatory and antioxidant properties, and is known to stimulate bile production, promote circulation and prevent allergies [88-89]. Alpha-tocopherol and Beta-carotene were found 0.04-0.07 mg/100 g and 35.0 µg/100 g respectively [90].
Carbohydrate: Of the various functional components in *Z. jujuba* fruits, polysaccharide is especially important because of its presence in large amounts and is mainly composed of many monosaccharides, with MW ranging from 3500 to 1,894,000 Da [91]. The jujuba date polysaccharides were shown to contain neutral and acidic polysaccharides, with the average MW of the former being 23,000 Da and the latter 263,000 Da. GC analysis revealed that 6 monosaccharides, namely, rhamnose, arabinose, xylose, mannose, glucose and galactose were present in polysaccharide fractions [92]. Tomoda *et al*., [93] isolated pectin A from *Z. jujuba* fruit. Pectin A was found to contain 2, 3, 6-tri-o-acetyl D lactose units. Pectin has a number of pharmaceutical properties such as binding bile acid, lowering plasma cholesterol and anti diarrhoeal properties [94-95].

Glycosides: Jujuboside A is a glycoside extracted from the seed of *Ziziphus jujuba Mill* var. spinosa (Bunge) Hu ex H F Chou, a Chinese herbal medicine, which has long been known as a sedative-hypnotic drug. In a study was conducted by Shou *et al*., inhibitory effects of Jujuboside A were reported on hippocampal formation in vivo and in vitro [96]. Jjujubosides A1, C and acetyljujuboside B1 were isolated from the seeds of *Ziziphus jujuba Mill*. They were found to inhibit the histamine release from rat peritoneal exudate cells induced by antigen-antibody-reaction [97].

Triterpenoides: Triterpenoid acids are one of the major active constituents in the fruit of *Z. jujuba*, which exhibited many biological activities such as cytotoxic [98], anti-complementary [66], anti- microbial [99], anti-plasmodial, anti-mycobacterial [100], anti-HIV [101], anti-inflammatory [102-103] and cyclooxygenase-2 inhibitory activities [66]. Until now, more than 15 triterpenoid acids were found in the fruit of *Z. jujuba*. It is known that the therapeutic effect of TCM is due to the synergic effect of its multiple chemical bioactive compounds [104]. A pentacyclic triterpenoid has been isolated from both bark and roots of *Ziziphus jujuba* [105]. Ceanothic acid, alphitolic acid, zizyberanal acid, zizyberanallic acid, epiceanothic acid, ceanothenic acid, betulinic acid, oleanolic acid and ursonic acid were determined in the dried fruit of *Ziziphus jujuba* (Dazao) which has been widely used as one of the traditional Chinese medicines [106]. As an important triterpenoid in semen *Ziziphi spinosae*, betulinic acid has been the subject of intense studies because of its biological
properties, especially its remarkable anti-melanoma, cytotoxic and anti-HIV activities [107].

**Phenolic Compounds:** Compounds from plant sources such as polyphenols act as primary anti-oxidants and free radical scavengers. Polyphenols exhibit multiple pharmacological properties such as anti-microbial, anti-allergenic, anti-ulcerogenic, anti-neo-plastic, and anti-inflammatory activities [108]. The polyphenol family comprises phenolic acids, stilbenes, chalcones, coumarins, cromones, lignans, flavonoids, isoflavonoids, neoflavonoids, and tannins. The polyphenol family has been shown to possess significant anti-oxidant capacities, while maintaining low toxicities [109].

In vitro research has shown that many natural polyphenols are better antioxidants than E and C vitamins [110]. Among the great family of polyphenols, flavonoids play an important role. Bioflavonoids are biologically active compounds that, once inside the human body, determine a positive biologic response. Bioflavonoids are recommended as supplement in preventing and treating those deficiencies that involve capillary fragility and permeability [111]. Seven phenolic compounds include catechin, caffeic acid, epicatechin, ferulic acid, rutin, \( p \)-hydroxybenzoic acid and chlorogenic acid, were isolated from fruits of jujuba selection. Main phenolics were rutin and apigenin-7-glucoside for leaves, and catechin and rutin for fruits [90].

**Lipids:** Among the four jujuba selections, lipid content of the fresh fruits ranged from 0.06% to 0.10% [50, 90]. The major fatty acids in all jujuba selections were oleic acid, linoleic acid, palmitic acid, palmitoleic acid [90, 112] and lauric acid, myristic acid, stearic acid, arachidic acid and docosanoic acid in Suanzaoren [112]. Unsaturated fatty acids consisted of 68.54–72.44% of the total fat in jujuba fruit [90]. Medium chain fatty acids were reported as the main fatty acids in several jujuba varieties from Spain [113]. Results from longest controlled feeding of medium-chain fatty acids studied to date suggest that short-term feeding of diets enriched by medium-chain fatty acids increases total energy expenditure [114]. Thus, a diet enriched with jujuba can have beneficial effects on human health. This fact has
relevance in countries in which jujuba consumption can represent an important part of the diet, such as occurs in some regions of India [115] and Iran.

6. **Ziziphus jujuba Health Benefits**

6.1 **Historical Use:** *Ziziphi jujuba* is believed to have various biological activities, it has been mentioned in the ancient famous Chinese medical book — Sheng Nong Ben Cao Jing, and has traditionally been used in oriental medicines [116]. For example, in Chinese traditional medicine, the dried fruits are prescribed as anodyne, anti-tumor, pectoral, refrigerant, sedative, stomachic, styptic and tonic. In Japan, the extracts of *Z. jujuba* are used to treat chronic hepatitis or distress and fullness in the chest and ribs. The local tribal people use the bark mixture of *Z. jujuba* to prevent the pregnancy [117].

6.2 **Sedative and sleep aid:** Insomnia is a common subjective complaint of inadequate sleep that affects 15-40 % of the general population. In a study the ethanolic extract of *Semen Ziziphi jujuba* induced anxiolytic effect at lower dose and sedative effect at higher dose [83]. The seeds of *Ziziphus jujuba Mill. var. spinosa* (Suanzaoren) HU have been used as a tonic and for treatment of insomnia in Chinese traditional medicine [51]. The sedative and hypnotic effects of three kinds of compounds include, flavonoids, saponins, and polysaccharides were compared by Jiang et al. They showed that saponins had a more effective sedative and hypnotic function than that of flavonoids and polysaccharides did not show a sedative and hypnotic effect [51]. Both saponins and fatty oil and also quantitative determination of them as a sedative and hypnotic effects are helpful to control the quality of Suanzaoren [112]. Hypnosis of *Semen Ziziphi Spinosae* may be related to the modulation effects on the cytokines. IL-1β and tumour necrosis factor-α (TNF-α) are the main sleep-regulatory cytokines, and IL-1, IL-4, IL-6 and IL-10 are sleep modulatory cytokines [118]. The effects of *Semen Ziziphi Spinosae* extracts could improved the levels of IL-6 and IL-1β and inhibited TNF-α in the serum of mice. Therefore, this traditional herb might treat insomnia using this effect of adjusting the cytokines in vivo [119].
6.3 Anti-complement: The complement system consists of over 20 serum proteins including nine complement components (C1 to C9) and their regulators, and is normally present in blood serum in an inactive form. The system is essential for the operation of the innate as well as the adaptive immune defence. The complement proteins can be activated through three cascade pathways: by the classical pathway, by the alternative pathway and by the antibody-independent lectin pathway [11]. Among eleven triterpenoids were isolated from the fruits of the *Ziziphus jujuba* Mill., 3-O-cis-p-coumaroyl maslinic acid, 3-O-trans-p-coumaroyl maslinic acid and oleanolic acid exhibited significant anti-complement activity [66]. Polysaccharides from *Ziziphus jujuba* are another bioactive constituents which may play an important role as anti-complementary activities [120].

6.4 Anti-inflammatory Benefits: Inflammation, a defense reaction of the body to eliminate or limit the spread of an injurious agent, is distinguished by edema formation, leukocyte infiltration and granuloma formation [121]. It is caused by the release of pro-inflammatory mediators like nitric oxide (NO) and prostaglandin (PGs) during generation of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX), respectively [122-123]. NO is produced from oxidation of L-arginine by iNOS following induction of pro-inflammatory mediators like prostaglandins, leukotrienes, adhesion molecules etc. [124]. Excessive or persistent inflammation causes a variety of pathological conditions, such as bacterial sepsis, rheumatoid arthritis and skin inflammation [125].

Anti-inflammatory effect of hydroalcoholic extract of *Ziziphus jujuba* fruits (ZJ) was investigated by using acute and chronic models of inflammation rat. Serum nitrite/nitrate was also estimated to determine the expression of nitric oxide. The serum nitrite/nitrate level was significantly increased after 7 days in the control group due to chronic inflammation, but was decreased by ZJ extract. Marked anti-inflammatory components of ZJ fruit in acute and chronic inflammation, include jujubosides, flavonoids and terpenes may produce the possibly inhibition nitric oxide expression. The anti-edematous effect of ZJ was significantly high during all the stages of inflammation, indicating the inhibition of release of COX, histamine and NO [14]. Another report documented the beneficial effect of ethanolic extract of leaves of
ZJ against carrageenan-induced paw edema in rat [126]. The jujubosides A1 and C and acetyljujuboside B1, isolated from seeds of ZJ, were reported to lower antigen–antibody reaction-induced histamine in rat peritoneal exudates [97]. The triterpenes and flavonoids from ZJ have been documented to have an anti-inflammatory effect [66, 81]. In an investigation ZJ essential oil showed strong anti-inflammatory effect than hydrocortisone and inhibited the inflammatory responses in animal model of chronic skin inflammation. Histological analysis clearly confirmed that ZJ essential oil might be beneficial as a good therapeutic agent for the treatment of various inflammatory diseases [127].

6.5 Antioxidant Benefits: Ziziphus jujuba has displayed anticancer activity in neoplastic human liver cells [15]. In a study it was shown that deproteinized polysaccharide isolated from Z. jujuba had antiproliferation effect on skin cancer [128]. In several studies using specific saponins, as well as ethyl acetate and water extracts of the fruit and bark, have investigated the potential cytotoxicity of jujuba. Apoptosis and differential cell cycle arrest are suggested to be responsible for the dose-dependent reduction in cell viability. Activity against certain human cancer cell lines has been demonstrated in vitro [83, 129-130].

Cytotoxicities of the triterpenoic acids extracted from Ziziphus jujuba were tested in vitro against tumour cell lines. The lupane-type triterpenes showed high cytotoxic activities. The cytotoxic activities of 3-O-p-coumaroylalphitolic acids were found to be better than those of non-coumaroic triterpenenoids. These results suggest that the coumaroyl moiety at the C-3 position of the lupane-type triterpene might play an main role in enhancing cytotoxic activity [63]. The triterponic acid, betulinic acid, extracted from Ziziphus jujuba and Ziziphus mauritiana, revealed selective toxicity against cultured human melanoma cells [131]. Betulinic acid is currently undergoing preclinical development. It is thought that betulinic acid may also be effective against other types of cancer. Recently, considerable in vitro evidence has demonstrated that betulinic acid is effective against small- and non-small-cell lung, ovarian, cervical, and head and neck carcinomas [132]. Published data suggest that betulinic acid induces apoptosis [131, 133] in sensitive cells in a p53- and CD95-independent fashion [134].
6.6 Antimicrobial Benefits: Numerous naturally occurring compounds found in plants, herbs, and spices have been shown to possess antimicrobial functions and provide as a source of antimicrobial agents against food-borne pathogens [135]. The efficacy of essential oil and methanol extracts from seeds of *Ziziphus jujuba* exhibited remarkable activity against some of the representative food-borne and spoilage pathogenic bacteria such as *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Escherichia coli*. This activity could be attributed to the presence of oxygenated mono and sesquiterpene hydrocarbons such as eucalyptol, caryophyllene, caryophyllene oxide. The antibacterial effect of various solvent extracts was comparable to the standard antibiotics. *Z. jujuba* mediated oil also contained high percentage of eugenol, isoeugenol, caryophyllene, eucalyptol, caryophyllene oxide, benzaldehyde and veridiflorol as earlier reported the major components of the various essential oils, which have enormous potential to inhibit microbial pathogens [16-17]. Gram-positive bacteria were shown to be more susceptible to the essential oil and various solvent extracts of *Z. jujuba* than Gram-negative bacteria. This is possibly due to the cell membrane of Gram-positive bacteria, which can interact directly with hydrophobic compounds of essential oils, whereas the external cell wall around the cell membrane of Gram-negative bacteria is hydrophilic and blocks the penetration of hydrophobic oil and inhibits the accumulation of essential oils in target cell membrane [136]. Therefore, essential oil and different extracts from seeds of *Z. jujuba* can be applied as natural preservatives in food against the well-known causal agents of food-borne diseases and food spoilage [137].

6.7 Antidiabetic Activity: As reported by Kim, *Ziziphus jujuba* seeds were effective on the improvement of the blood glucose, lipid compositions in serum of dietary hyperlipidemic rats [12]. Furthermore, Glombitza *et al.* [138] found that the butanol extract of *Ziziphus spina-christi* leaves or its main saponin glycoside, christinin-A, improved glucose utilization in diabetic rats, but not in normal rats after 1 and 4 weeks of treatment. Serum insulin and pancreatic cAMP levels showed a significant increase in diabetic rats treated for a period of 4 weeks. In a study conducted by Avizeh *et al.* treatment with *Ziziphus spina-christi* extract reduced blood glucose of dogs, while serum insulin level increased. They have stated that presence of saponin
in Ziziphus fruit may have glucagon decreasing effect and may enhance glucose utilization and lower blood glucose [139]. It is reported that saponin stimulates insulin release from pancreas. A group of saponins, called gypenosides (phanoside) release nitric oxide from endothelial cells [140]. It has been demonstrated that nitric oxide increases insulin release from pancreatic β cells [141]. Phanoside is a potent initiator and potentiator of insulin secretion both in vivo and in vitro in the rat [140]. The tannins in Ziziphus fruit have antioxidative effect. Oxidative stress is one of the important factors in tissue injury in diabetes mellitus [142]. Oxidative stress might result from increased generation and or insufficient removal of ROS. Oxidative stress state is associated with multiple factors including increasing the levels of glucose, triglycerides and decreasing HDL levels in type 2 diabetes based on the association analysis of clinical indexes and oxidative stress indexes [142]. Excessive ROS generation causes the damage of proteins, lipids and DNA, furthermore, expand to the cellular dysfunctions [143]. It has been proposed that oxidative stress in monocytes might be a crucial factor in initiating and processing multiple diabetic complications. It is well known that the highly activated circulating monocytes are recruited to the vessel wall and differentiated into macrophages. These monocytes/macrophages are likely a rich source of superoxide anion in the vessel wall, which results in the formation of atherosclerotic lesions [142].

These powerful antioxidants may protect beta cells and increase insulin secretion in diabetic dogs. Besides, tannins may inhibit insulin degradation and improve glucose utilization [144]. The relative highly content of fructose (78% of the total free sugars) makes Ziziphus fruit valuable for diabetic patients [145].

The effects of methanol extracts of Ziziphus spina christi (ZSC) and Ziziphus jujuba (ZJ) roots for the treatment of alloxan diabetic rats were reported by Hussein et al. ZJ significantly reduced serum total lipids, triglycerides, total cholesterol and lipid peroxides low density lipoprotein cholesterol, but no significant difference on high density lipoprotein cholesterol. Mean while, ZSC caused noticeable decreases in TC, TG and LP compared with the untreated diabetic rats. ZJ significantly decreased alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin (TB) in diabetic rats. Serum creatinine and urea showed a significant reduction in diabetic rats.
treated with ZSC extract. Both extracts produced no significant changes in all studied parameters except for a significant reduction of serum lipid peroxides and urea by ZJ extract as compared to untreated diabetic control. They revealed that both extracts of ZSC and ZJ have beneficial effects on diabetic rats. Besides, they were safe towards liver and kidney functions. The effect of ZJ was more pronounced than that of ZSC [15].

6.8 Immunological Activity: Several triterpene oligoglycosides from medicinal herbs or foodstuffs with tonic and nutritive effects were found to show immunological adjuvant activity [146]. There is some research papers related to the immunobiological activities of polysaccharides from Chinese jujuba in the form of mixtures or the purified fractions. Zhao et al. characterized crude water-soluble polysaccharides (WSPs) from leaves, fruits and flowers of Chinese Jujuba, and found all of WSPs had immunobiological activities, especially in fruits and flowers [18]. The polysaccharides from Ziziphus Jujuba cv. Jinsixiaozao (ZSP), one of the major Chinese jujuba varieties, were extracted and purified sequentially so that its water-soluble immunobiological fractions were screened. The crude ZSP was found to significantly increase thymus and spleen indices in mice, improve the proliferation of splenocytes and peritoneal macrophages, and have potential anti-complementary activity. Two fractions of ZSP, coded ZSP3c and ZSP4b both significantly increased the proliferation of spleen lymphocyte. ZSP3c was rich in pectin with a degree of esterification of 49%, which may be related to its stronger immunological activity [147]. Zhao et al. isolated two pectic polysaccharides from Ziziphus jujuba Mill. cv. Jinsixiaozao Hort, and found that one of polysaccharides induced rat spleen cells proliferation in a dose-dependent manner. According to their structures, rhamnogalacturonan and side chains proposed the major contributors in stimulating the immune responses [148].

6.9 Hepatoprotective Effect: Liver disease is a serious health problem because the liver is an main organ for the biotransformation and detoxification of endogenous and exogenous harmful materials. It is well known that free radicals cause cell damage through the mechanisms involving in lipid peroxidation with consequent tissue injury, especially liver damage [149]. Some antiviral drugs, which are using to treat liver
disease, have been shown to have potential adverse effects, especially when administrated for long-term [150]. For this reason, natural antioxidants have been a substantial increase as more valuable and safe dietary ingredients for alternative therapies of liver disease [151].

Hydroquinone (HQ) is a myelotoxin that is found in many foods and formed through the metabolism of benzene. HQ is genotoxic in several *in vitro* and *in vivo* test systems, inducing micronuclei (MN), sister-chromatid exchange (SCE), and chromosomal aberrations. The protective effect of *Ziziphus jujuba* and *Origanum majorana* extracts against HQ-induced genotoxicity in male mice were explored by Ghaly *et al*. The results indicated that both extracts exhibited a protection against HQ-induced cytogenesis and histological changes. Moreover, *Z. jujuba* extract was effective than *O. majorana* extract. It could be concluded that both extracts are useful especially for people who are occupationally exposed to benzene or its metabolites [19].

Ischemia and reperfusion (I/R) injury in the liver remains an important clinical problem during liver surgery, transplantation, and shock. Free oxygen radicals, such as superoxide, hydrogen peroxide, and hydroxyl radical, as well as a nitric oxide (NO) burst have been shown to be involved in the pathogenesis of I/R-related liver injury [152]. *Ziziphus Jujuba* (ZJ) is a key constituent in the Chinese herb that is known for its hepatoprotective effect and traditionally, is used prophylactically for liver diseases. *Ziziphus Jujuba*, which has antioxidant effects to scavenge oxygen radicals, significantly reduced liver injury by decreasing oxygen radicals. ZJ also increased endogenous nitric oxide (eNOS) expression [153] which could scavenge oxygen radicals, reducing inflammation and inducible nitric oxide synthase (iNOS) expression. Controversy exists with respect to the effects of NO on liver injury. It appears that NO plays a paradoxical or dual role in hepatic injury due to various causes, depending on the experimental conditions, the amount of NO production, and the nitric oxide synthase (NOS) isoforms. ZJ attenuates NO release possibly due to its anti-inflammatory effects, reducing nitrosative stress. In summary, reperfusion liver injury induces oxidative and nitrosative stress involving systemic inflammatory responses. Pretreatment with ZJ extract, which shows antioxidant and anti-
inflammatory effects, significantly attenuated I/R-induced liver injury and consequent inflammatory responses [154].

Methanolic extract of *Ziziphus jujuba* fruits (MEZJ) was studied in rats induced hepatic damage. The low and medium doses (250 mg/kg and 500 mg/kg) of MEZJ significantly inhibited the acute elevation of biomarkers in blood of hepatic injury include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin levels in serum. The low and medium dose of MEZJ also increased the activities of SOD and catalase in the liver tissue homogenate that probably indicate hepatoprotective activity due to its antioxidant effect [155]. Another study was conducted to investigate the protective effect of *Ziziphus jujuba* fruit (FZJ) against hepatic injury. Results after administrated the FZJ at the dose of 200mg/kg, significantly decreased ALT and AST, and attenuated histopathology of hepatic injury. Oxidative stress include malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and reduced glutathione (GSH) in hepatic tissue were improved. These results of above study indicated that hepatic protective effects of FZJ were very relevant to modulate the oxidative stress in hepatic injury [156].

Hepatoprotective effect of the polysaccharides from *Ziziphus jujuba* cv. *Shaanbeitanzao* (ZSP) was demonstrated in mice. Administration of ZSP (400 mg/kg) significantly decreased the activities of CCl4-elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactic dehydrogenase (LDH) in serum, and hepatic malondialdehyde (MDA) level. Mice treated with ZSP showed a better profile of hepatosomatic index (HI) and antioxidant system with normal glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) activities in liver. The authors suggested that adequate consumption of *Ziziphus jujuba* cv. *Shaanbeitanzao* and its polysaccharide extracts might has a favorable effect on maintaining or progressing antioxidant systems and the liver functions of the host [157].

6.10 **Cardiovascular Effect:** Nitric oxide (NO) produced by endothelial NO synthase (eNOS) is an important vasodilator and acts a protective physiological role in the vasculature. Besides its role in controlling blood pressure, NO protects the blood vessels from thrombosis by inhibiting platelet aggregation and adhesion. In
addition, endothelial NO possesses multiple antiatherosclerotic properties [158]. Due
to the antithrombotic, antiatherosclerotic, and anti hypertensive properties of
endothelial NO, the eNOS enzyme could be an interesting aim for the prevention or
therapy of cardiovascular disease. A dysfunctional eNOS has been referred to as
eNOS “uncoupling” [159]. The main reason for eNOS uncoupling is a deficiency of
the essential eNOS cofactor (6R)-5,6,7,8-tetrahydro-L-biopterin (BH4) [160].
Oxidation of BH4 due to NADPH oxidase-mediated vascular oxidative stress may
represent a major cause of BH4 deficiency in many cases [159]. Suppression of
oxidative stress by down- regulating the expression or activity of vascular NADPH
oxidase has been shown to restore eNOS functionality [161-162]. Therefore, a
correction of eNOS uncoupling combined with up-regulation of eNOS expression
may be a hopeful therapeutic strategy for cardiovascular disease. Pharmacological
studies revealed that *Zizyphi Spinosi semen* (ZSS) has potent actions on the
cardiovascular system, such as antiarrhythmic and blood pressure lowering effects
[20]. The active constituents of ZSS include triterpenoids (such as betulin and
betulinic acid) [163], saponins, flavonoids, alkaloids, and fatty acids [20, 112].
Damage of cultured neonatal rat myocardial cells by deficit of oxygen and glucose
was noticeably reduced by ZSS total saponins [164]. ZSS protects cardiomyocytes
from ischemic injury. Intravenous injection of an aqueous solution of ZSS extract
obviously decreased blood pressure in anesthetized rats, dogs, and cats with no
significant effect on the coronary blood flow, heart rates, or myocardial contractility
[165].

Treatment of hypercholesterolemic rabbits with ZSS for 3 months resulted in a
decrease of total cholesterol, triglyceride, LDL, and atherosclerosis and an increase in
HDL [166]. In a systematically study the effect of ZSS and its constituents on the
gene expression of eNOS was investigated. They found that ZSS increases eNOS
promoter activity, eNOS mRNA, and protein expression, as well as NO production in
human endothelial cells [153]. Treatment of human endothelial cells with betulinic
acid resulted in a significant up-regulation of eNOS mRNA and protein expression.
Thus, betulinic acid is probably one of the compounds responsible for the eNOS up-
regulation produced by ZSS.
In diseased human coronary arteries, approximately 60% of vascular superoxide is derived from NADPH oxidases [167]. Interestingly, betulinic acid significantly reduced the expression of NADPH oxidase catalytic subunits Nox4 and p22phox, which is associated with a reduction in ROS production. Therefore, betulinic acid possesses a dual protective action on the vasculature. i) It up-regulates eNOS expression, thereby producing more eNOS protein, and ii) it down-regulates NADPH oxidase, thereby maintaining the up-regulated eNOS enzyme in a functional state. Thus, the combination of eNOS up-regulation and NADPH oxidase down-regulation may result in enhanced levels of bioactive NO and thus vascular protection.[153].

The aqueous solution of Ziziphus jujuba seeds has been reported to have a considerable antagonistic effect on EKG changes of BaCl2-induced cardiac arrhythmias of rats (p< 0.01) and also improved apparently those changes caused by aconitine (p<0.01). Cardiac ischaemic EKG changes induced by pituitrin were improved (p<0.01) by this preparation (ip 4 ml/kg or iv 1.5ml/kg) as well [168].

6.11 Gastrointestinal Effects: The prevalence of chronic constipation ranges from 12% to 19% and is characterized by infrequent bowel movements (<3 per week) lasting more than 3 months and typically for many years [169]. Chronic constipation is a long-term condition that dominates both physiological and psychological aspects of the individual [170].

Jujuba fruit has traditionally been used as a paste, puree, or soup to enhance digestion. In hamster experiments, water soluble extract of Chineses jujuba shortened GI transit time, elevated total short chain fatty acid concentrations in cecum, increased fecal moisture content, reduced daily fecal ammonia output, reduced cecal ammonia, decreased the activities of β-D-glucuronidase, β-D-glucosidase, mucinase and urease in feces. Therefore, adequate consumption of water soluble extract of jujuba might exert favorable effects on improving the gastrointestinal milieu and reducing the exposure of intestinal mucosa to toxin ammonia and other harmful compounds [21]. In a clinical trial study, the symptoms of patients with chronic idiopathic constipation improved with daily consumption of jujuba extract (average, 20 drops per day) versus pl acebo. Jujuba extract may offer a safe natural laxative option. Objectively, GI
transit time improved significantly in the study group, and subjectively, the majority of patients expressed satisfaction with the treatment. At present, it is not known which compound is the active ingredient in improving constipation. It could be a form of anthraquinone, as contained in senna and other plant-based laxatives. Hence, *Z. jujuba* extract is secure and effective for chronic idiopathic constipation and can be safely recommended for at least 12 weeks of treatment [171].

The available literature indicates that, there is a range of potentially useful medicinal compounds in Chinese date. The value of such constituents in health products and supplements is undisputed and the hardy nature of jujubas and their wide geographical range can provide a potentially cheap and more accessible source of such compounds for traditional medicine. However, no reports on the lipid lowering potential of *Ziziphus jujuba Mill.* in human were available.
Chapter- II

Dyslipidemia
CHAPTER II

Dyslipidemia

1. **Introduction:** Cardiovascular diseases (CVD) are the most prevalent cause of death and disability in both developed as well as developing countries [172]. South Asians that include Bangladeshis, Indians, Nepalese, Pakistani and Sri Lankans have the highest rates of Coronary Artery Disease (CAD) among all the ethnic groups, irrespective of their religious affiliations, lifestyle, diet or the country of residence [173-174]. According to National Commission on Macroeconomics and Health (NCMH), a Government of India undertaking, there would be around 62 million patients with CAD by 2015 in India and of these, 23 million would be patients younger than 40 years of age [175]. Heart disease and stroke are usually due to atherosclerosis of large and medium sized arteries and dyslipidemia has been found to be one of the most important contributing factor [176]. Hypertension, smoking, diabetes, obesity, physical inactivity, and atherogenic diets have all been identified as modifiable risk factors for heart disease. Age, male gender, menopaus status and a family history of premature coronary heart disease (CHD) have been identified as nonmodifiable risk factors [176]. In California, Asian Indians have the highest rate of hospitalization for CHD, and Chinese have the lowest rate. Intermediate rates were reported for whites, Japanese, and Filipinos [177]. The racial/ethnic differences in susceptibility to CHD appear to have a genetic basis. It is essential that physicians recognize the racial/ethnic differences and adjust lipid management strategies appropriately for each subpopulation [33, 178].

2. **Historical Perspective:** The creation in 1948 of the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH), might be considered the advent of the contemporary study of atherosclerosis in the United States. The new institute reorganized the Framingham Heart Study in 1949, creating one of the first main efforts dedicated to the study of chronic disease. Based on Framingham Heart Study results reported in 1961, the concept of risk factors for coronary heart disease was obviously established. Hypertension and hypercholesterolemia were initially identified as major contributors to cardiovascular disease. Smoking was identified as a risk factor for cardiovascular disease in the
Surgeon General’s report in 1964 [179]. While the crucial role of cholesterol in the development of atherosclerosis was recognized in the 1950s, it was not until 1988 that the NHLBI issued its first clinical practice guidelines under the auspices of the NCEP. The guidelines were updated in 1993, and the “Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,” also recognized as Adult Treatment Panel (ATP III), was issued in 2001 [176].

3. Assessing Risk: Cholesterol is a lipid that is present in cell membranes and is the precursor for steroid hormones and bile acids. Cholesterol is found in the blood in distinct particles containing both lipids and proteins, and the particles are called lipoproteins. Lipoproteins found in humans are divided into classes according to their flotation constants or densities. Three major classes are found: low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very-low-density lipoproteins (VLDL). LDL cholesterol contains cholesterol and a single protein or apolipoprotein, apoB-100. LDL constitutes about 60% to 70% of total serum cholesterol. LDL is the major atherogenic lipoprotein, and is the primary target for cholesterol lowering therapy. The ATP III classification of total cholesterol and LDL cholesterol serum levels are listed in Table 1. HDL contains cholesterol and apo AI and apo AII apolipoproteins. HDL constitutes about 20% to 30% of total serum cholesterol. HDL is thought to protect against the development of atherosclerosis. The ATP III Classifications of HDL Cholesterol serum levels are listed in Table 1. Triglycerides are transported in the blood as chylomicrons following absorption from the small intestine, or as a component of VLDL if synthesized by the liver. The ATP III classification of serum triglycerides is listed in Table 1. VLDL is triglyceride-rich lipoprotein and constitutes about 10% to 15% of total serum cholesterol. VLDL has several apolipoproteins, including apo B100, apo CI, apo CII, apo CIII and apo E. VLDL is a precursor of LDL. Some forms of VLDL are actually partially degraded lipoproteins called VLDL remnants. VLDL remnants appear to promote atherosclerosis, similar to LDL. Since both VLDL remnants and LDL are atherogenic, they may be combined to estimate risk prediction. The sum of VLDL + LDL is called non-HDL cholesterol.
Table 1. ATP III Classification of Total Cholesterol, LDL Cholesterol and HDL Cholesterol

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dl)</th>
<th>LDL Cholesterol (mg/dl)</th>
<th>HDL Cholesterol (mg/dl)</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>&lt;100</td>
<td>&lt;40</td>
<td>&lt;150</td>
</tr>
<tr>
<td>200-239</td>
<td>100-129</td>
<td>≥60</td>
<td>150-199</td>
</tr>
<tr>
<td></td>
<td>Near Optimal/Above Optimal</td>
<td></td>
<td>Borderline High</td>
</tr>
<tr>
<td>≥240</td>
<td>130-159</td>
<td></td>
<td>200-499 High</td>
</tr>
<tr>
<td></td>
<td>160-189</td>
<td></td>
<td>≥500</td>
</tr>
<tr>
<td></td>
<td>≥240</td>
<td></td>
<td>Very High</td>
</tr>
</tbody>
</table>

Lipoprotein (a) [LP (a)] has been categorized as an emerging lipid risk factor by ATP III. LP (a) represents a class of LDL particles that have as a protein moiety apolipoprotein B-100 linked to another protein moiety, apolipoprotein (a). LP (a) is structurally similar to plasminogen, but has no thrombolytic activity. Several studies report a strong association between LP (a) levels and CHD risk. LP (a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than those revealed by LDL, HDL, and triglyceride levels [180]. An elevated LP (a) level presents the option to raise a person’s risk to a higher level and to target the person for a more aggressive treatment. The optimal level of LP (a) should be no greater than 20 mg/dl [181-182].

ATP III has classified homocysteine as an emerging non-lipid risk factor. While the link between homocysteine and CHD is not well understood, some hold that the association is strong enough to make it a direct target of therapy [183]. Measurement of homocysteine remains an option in selected cases, such as in someone with a strong family history of premature CHD, yet who is an otherwise low-risk patient. The optimal level of homocysteine should be no higher than 10 mol/L [184].
Major risk factors identified by ATP III are listed in Table 2 [185]. The category of highest risk consists of CHD and CHD risk equivalents. CHD risk equivalents carry a risk for main coronary events equal to that of established CHD. Coronary heart disease risk equivalents include: Other forms of atherosclerotic disease, Diabetes, Multiple risk factors that confer a 10-year risk >20%.

Table 2. ATP III Nonlipid Risk Factors for CHD

<table>
<thead>
<tr>
<th>Modifiable Risk Factor</th>
<th>Nonmodifiable Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Menopausal status</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>Age</td>
</tr>
<tr>
<td>Thrombogenic/Hemostatic State</td>
<td>Male Gender</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Family History of Premature CHD</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td></td>
</tr>
<tr>
<td>Atherogenic Diet</td>
<td></td>
</tr>
</tbody>
</table>

The common pattern of dyslipidemia seen in Asian Indians when compared to the lipid profile of white Americans is listed in Table 3 [33, 186-187]. Asian Indians tend to have higher levels of triglycerides, lower HDL levels, and higher levels of LP (α). In addition, the higher CHD risk in this population may be related to a higher prevalence of the metabolic syndrome, insulin resistance, and diabetes.

The metabolic syndrome has become increasingly common in the United States, and is common in the Asian Indian population in the United States. The metabolic syndrome is thought to be associated with genetic factors, overweight/obesity, and physical inactivity. The syndrome is characterized by abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, glucose intolerance, prothrombotic state, and proinflammatory state [176].
Table 3. Pattern of Dyslipidemia among Asian Indians Relative to American Whites

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Relative Serum Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholestrol</td>
<td>Similar</td>
</tr>
<tr>
<td>LDL</td>
<td>Similar</td>
</tr>
<tr>
<td>Small Dense LDL</td>
<td>Similar</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Higher</td>
</tr>
<tr>
<td>HDL</td>
<td>Lower</td>
</tr>
<tr>
<td>LP (a)</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Table 4 lists risk factors that are associated with the metabolic syndrome [176]. Total cholesterol levels and LDL levels are correlated with extent and severity of CHD in Asian Indians as in whites. But at any given total cholesterol or LDL level, Asian Indians have a higher CHD risk than whites [188]. Therefore, Asian Indians with dyslipidemia should be treated as aggressively as if they had a CHD risk equivalent—similar to the treatment of patients with diabetes or heart disease. Thus, while a total cholesterol level of <200 mg/dl is desirable according to the Framingham model for those with 0 to 1 risk factor, the goal for the Asian Indian population should be <160 mg/dl. An LDL level of <160 mg/dl is appropriate for most Americans with 0 to 1 risk factor, but a level of <100 mg/dl is optimal for Asian Indians [189]. In a update of ATP III, Grundy S. et al [48] issued modifications to footnote the ATP III treatment algorithm as follows: In high risk patients, the recommended LDL-C goal is <100 mg/dl, but when risk is very high, an LDL-C goal of <70 mg/dl is a therapeutic option. Among factors that place patients at "very high risk" are the presence of established CVD plus, multiple major risk factors, diabetes mellitus, metabolic syndrome and patients with acute coronary syndromes.

HDL levels of 60 mg/dl are considered optimal in both whites and Asian Indians. HDL levels are considered low when they drop below 40 mg/dl. However, most experts consider a level <50 mg/dl to be low in women. In fact, HDL levels <50 mg/dl are used as one of the diagnostic criteria for the diagnosis of metabolic syndrome in women by the ATP III. A study of Asian Indians living in the United
States found that 54% of men had an HDL level below 40 mg/dl, and 68% of women had levels below 50 mg/dl [190-191].

The acceptable “normal” level of triglycerides was decreased from <200 mg/dl in the ATP II report to <150 mg/dl in the ATP III classification. In the United States, 43% of Asian Indian males and 24% of Asian Indian females have levels more than 150 mg/dl [190-191]. The CHD risk among Asian Indians is at least 2-fold greater than other populations, even when adjusted for all conventional risk factors and the various components of the metabolic syndrome [187, 192-194].

Lipoprotein (a) is still considered an emerging risk factor in the US population at large, but shows to be a main risk factor in Asian Indians [33, 195-196]. A high level of LP (a) is the most prevalent dislipidemia in patients with premature CHD. LP (a) levels are governed almost exclusively by race, ethnicity, and genetics, unlike other lipids, where the levels are influenced by age, gender, diet, and other environmental factors [197-199]. Although LP (a) levels >30 mg/dl are generally considered the threshold at which high risk of premature CHD increases rapidly, levels below 20 mg/dl are considered optimum, mainly in Asian Indians [196]. Studies of Asian Indians in North America found that 25% to 50% of sampled populations have levels >30 mg/dl. High levels of LP (a) were also reported for Asian Indians living in Canada, Singapore, the United Kingdom, and India [200]. The multiplicative effects of elevated LP (a) are significant. Modestly elevated LP (a) levels of 20 mg/dl to 30 mg/dl are related to a 2- to 3-fold higher risk of MI or restenosis following coronary angioplasty and bypass surgery [181, 201]. This risk increases 10-fold when an LP (a) level >50 mg/dl happens in persons with high cholesterol levels. The risk of MI increases 100-fold when LP (a) levels >55 mg/dl are accompanied by low HDL and a high ratio of total cholesterol to HDL [202-203].

When combined with concomitant elevation of triglycerides, and LDL, and decreases in HDL concentrations, the pathophysiological effects of high LP (a) level are exponentially increased [203]. This “deadly lipid quartet,” commonly present in Asian Indians, usually results from affluent lifestyles led by immigrants, as well as those living in urban areas in India [203].
### Table 4. Clinical Identification of the Metabolic Syndrome.

The Presence of Three or More Factors Confirm the Diagnosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td></td>
</tr>
<tr>
<td>Men (Whites)</td>
<td>Waist Circumference: &gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>(Asian Indian)</td>
<td>&gt;90 cm (&gt;36 in)</td>
</tr>
<tr>
<td>Women (Whites)</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>(Asian Indian)</td>
<td>&gt;80 cm (&gt;32 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dl or drug treatment for hypertriglyceridemia</td>
</tr>
<tr>
<td>HDL Cholestrol</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dl or drug treatment for low HDL cholesterol</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dl or drug treatment for low HDL cholesterol</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>≥130/85 mmHg or on antihypertensive drug treatment in patients with a history of hypertension</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>110-125 mg/dl or on drug treatment for elevated blood glucose level</td>
</tr>
</tbody>
</table>

As discussed earlier, in treating dyslipidemia, Asian Indian ethnicity should be considered a CHD risk equivalent, with an LDL goal of <100 mg/dL [204]. Table 5 lists an approach to the patient for evaluating risk for CHD and for implementing therapy if necessary.
Table 5. Approach to the Patient with Hyperlipidemia for Evaluating Risk for CHD and for Implementing Therapy

- Rule out secondary dyslipidemia (Diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, drug-induced)
- Perform risk assessment
- Encourage smoking cessation
- Control hypertension and diabetes
- Implement therapeutic lifestyle changes (improved diet, weight loss, increased physical activity)
- Achieve LDL-cholesterol goal with statin therapy
- Achieve other lipid (HDL, triglycerides, Lp[a]) and non-lipid (homocysteine) goals with niacin or Niaspan.
- Monitor response and adherence to therapy every 4 to 6 months

The optimal level of risk factors for Asian Indians is listed in Table 6. This chart includes desirable goals for blood lipids and non-lipid risk factors. Note also that the optimum waist size for Asians, including Asian Indians, has been adjusted downward according to the recommendations of the World Health Organization (WHO) [205]. This takes into account the cut off point at which metabolic abnormalities increase rapidly.

Table 6. Optimum Level of Risk Factors for Asian Indians

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Lp (a) (mg/dL)</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Blood Pressure (mm Hg)</td>
<td>&lt;120/80</td>
<td>&lt;120/80</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>&lt;110</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Waist Size (cm/in)</td>
<td>&lt;90/36</td>
<td>&lt;80/32</td>
</tr>
</tbody>
</table>
4. **Etiology:** Dyslipidemia is a heterogeneous disorder with multiple etiologies. The most common dyslipidemia causes have been described as follow:

**4.1 Primary Causes:** Several monogenic disorders have been defined that lead to different type of dyslipidemias, but for many cases, the etiology is polygenic (Table 7). These disorders affect plasma lipoprotein levels by overproduction of lipoproteins and/or decreased clearance. All the known genes defective in patients with monogenic hypercholesterolemia’s are involved in the receptor-mediated uptake of low-density lipoproteins (LDL) by the LDL receptor (LDLR) in the hepatocytes [206]. Studies reveal that, among patients meeting the clinical criteria for monogenic hypercholesterolemia, LDLR mutations have been reported in 52–76% of patients [207-208]. Loss of function or reduced LDLR number in the hepatocytes results in reduced clearance of plasma LDL and a 2- to 3-fold elevation in LDL cholesterol levels in heterozygous familial hypercholesterolemia (FH) patients. Approximately half of these patients develop tendon xanthomas, xanthelasmas, and premature corneal arcus, and coronary heart disease (CHD) occurs in the fourth or fifth decades. Homozygous or compound heterozygous patients have a higher than 5-fold enhance in plasma LDL cholesterol levels and often develop severe atherosclerosis before the age of 20 yr [206].

<table>
<thead>
<tr>
<th>Elevated LDL Cholesterol</th>
<th>Low HDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL receptor deficiency</td>
<td>Apo A1 deficiency</td>
</tr>
<tr>
<td>Familial homozygous hyperlipidemia</td>
<td>Apo A1 mutation</td>
</tr>
<tr>
<td></td>
<td>LCAT deficiency (Partial or complete)</td>
</tr>
<tr>
<td></td>
<td>Tangier’s disease</td>
</tr>
<tr>
<td></td>
<td>Familial hypoalphalipoproteinemia</td>
</tr>
</tbody>
</table>

**4.2 Secondary Causes:** Dyslipidemia is more often secondary to other causes than a primary genetic defect (Table 8). Even in patients with known genetic disorders, it is important to consider secondary factors that may affect lipid levels. These include obesity; lifestyle influences such as diet, exercise, smoking, and alcohol use;
endocrine disorders such as diabetes mellitus and hypothyroidism; and liver and renal diseases. Another important cause for elevated lipids is the use of pharmacological agents. Drugs such as diuretics, β blockers, glucocorticoids, retinoic acid derivatives, and interferons α, β, and γ are well known to increase serum triglycerides. Cyclosporine can increase LDL cholesterol levels, and sirolimus and HIV 1 protease inhibitors can cause severe hypertriglyceridemia. Bexarotene, a retinoid X receptor selective retinoid, causes hypertriglyceridemia in up to 80% of patients [209]. Tamoxifen, by virtue of its estrogenic effects, can also cause severe hypertriglyceridemia in susceptible individuals [210] but reduces LDL cholesterol levels. Aromatase inhibitors can modestly raise LDL cholesterol levels, especially in comparison with tamoxifen [211-212]. Severe hypertriglyceridemia has also been reported anecdotally with the use of asparaginase, capecitabine, and propofol [213-215].”

<table>
<thead>
<tr>
<th>Elevated LDL Cholesterol</th>
<th>Low HDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>High fat intake</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Obesity or weight gain</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>Tobacco use</td>
</tr>
<tr>
<td>Anabolic Steroids</td>
<td>Beta Blocker Therapy</td>
</tr>
<tr>
<td>Progestins</td>
<td>High fat diet</td>
</tr>
<tr>
<td>Obstructive Hepatobiliary Disease</td>
<td>Anabolic Steroids</td>
</tr>
<tr>
<td></td>
<td>Progestins</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics</td>
</tr>
</tbody>
</table>

**a. Diabetes:** Macrovascular disease, i.e. coronary heart disease (CHD), cerebrovascular disease and peripheral vascular disease are the most frequent causes of morbidity and mortality in patients with type 2 diabetes (T2D). Diabetes mellitus confers a 2- to 4-fold increase in cardiovascular risk compared with the general population [216]. Dyslipidemia belongs together with hypertension and
hyperglycemia to the modifiable risk factors for atherosclerosis in diabetic patients [217]. Dyslipidemia in T2D is characterized by high plasma triglyceride and decreased HDL cholesterol level, as well as by predominance of small, dense LDL particles. Apolipoprotein B (apoB) is also increased, thus, this type of dyslipidemia shares some common features with familiar combined hyperlipidemia. Increased plasma apoB level reflects increased number not only of LDL particles, but also of IDL and VLDL particles [218]. Increased number of triglyceride-rich lipoprotein particles was shown to be related to the severity of coronary atherosclerosis [219]. Dyslipidemia is related to insulin resistance and as a part of metabolic syndrome it precedes the clinical diagnosis of diabetes by years [219]. Several groups have shown that Asian Indians are predisposed to metabolic syndrome and insulin resistance, which are often characterized by low HDL cholesterol levels and hypertriglyceridemia [29-30, 220]. Atherogenic dyslipidemia may, therefore, be more prevalent in this racial group compared with whites.

b. Alcohol overuse: Alcohol exerts several effects on lipid levels, including increasing the serum triglyceride and HDL cholesterol levels. Its effect on LDL cholesterol appears to be minimal. Since excessive alcohol causes various adverse effects, including hepatic toxicity, cardiomyopathy, motor vehicle crashes and extensive psychosocial consequences, it is not recommended for the prevention of coronary heart disease [221].

c. Chronic Kidney Disease (CKD): Patients with CKD have minor proatherogenic lipid abnormalities that are treatable with readily available therapies, yet many clinicians are reluctant to treat these patients aggressively, citing concerns about safety or lack of evidence suggesting clinical advantage when using drugs in this population. The link between dyslipidemia and increased CVD risk in patients with CKD has been difficult to establish in large part due to the myriad other cardiovascular risk factors observed in patients with CKD, including increased oxidative stress, inflammation, physical inactivity, anemia, vascular calcification, endothelial dysfunction and reduced nitric oxide availability. CKD causes profound dysregulation of lipoprotein metabolism, resulting in multiple lipoprotein abnormalities [222]. Dyslipidemia develops during the early stages of CKD, and
significant changes in apolipoproteins usually lead changes in plasma lipid levels [223-224]. Depressed HDL levels and increased triglyceride rich lipoproteins are the major lipid abnormalities. The increased plasma triglyceride levels can be explained in part by significant increases in plasma Apo C-III levels. Apoprotein C-III is a potent inhibitor of the enzyme lipoprotein lipase, which is responsible for the degradation of triglyceride-rich particles [225].

d. **Hypothyroidism:** It is well known that alterations in thyroid function result in changes in the composition and transport of lipoproteins [226-228]. Therefore, hypothyroidism constitutes a significant cause of secondary dyslipidemia [229-230]. In general, overt and subclinical hypothyroidism is associated with hypercholesterolemia mainly due to elevation of low density lipoprotein (LDL) cholesterol levels, whereas high density lipoprotein (HDL) cholesterol concentration is usually normal or even elevated [228, 231]. On the other hand, hyperthyroidism (both overt and subclinical) is accompanied by a decrease in serum levels of total, LDL and HDL cholesterol [232]. These changes in the lipid profile are explained by the regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism. Specifically, the thyroid hormone stimulates the hepatic de novo cholesterol synthesis by inducing the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol [233]. This results in an enhanced intracellular cholesterol concentration in hyperthyroidism and a decreased one in hypothyroidism. Additionally, thyroid hormones activate the LDL receptors; the promoter of the LDL receptor gene contains a thyroid hormone responsive element (TRE) which allows the triiodothyronine (T3) to upregulate the gene expression of the LDL receptor [234]. Moreover, thyroid hormones stimulate the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl esters from HDL2 to the very low density lipoproteins (VLDL) and triglycerides in the opposite direction [235]. Finally, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the triglyceride-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL2 to HDL3 [236].
5. Diagnosis: Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements (lipid profile) include total cholesterol (TC), TGs, HDL cholesterol, and LDL cholesterol. Dyslipidemia is suspected in patients with characteristic physical findings or complications of dyslipidemia (eg, atherosclerotic disease). Primary lipid disorders are suspected when patients have physical signs of dyslipidemia, onset of premature atherosclerotic disease (at <60 yr), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dl (> 6.2 mmol/L).

   a. Lipid profile measurement: TC, TGs, and HDL cholesterol are measured directly; TC and TG values reflect cholesterol and TGs in all circulating lipoproteins, including chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. TC values vary by 10% and TGs by up to 25% day-to-day even in the absence of a disorder. TC and HDL cholesterol can be measured in the nonfasting state, but most patients should have all lipids measured while fasting for maximum accuracy and consistency. Testing should be postponed until after resolution of acute illness, because TGs increase and cholesterol levels decrease in inflammatory states. Lipid profiles can vary for about 30 days after an acute MI; however, results obtained within 24 h after MI are usually reliable enough to guide initial lipid-lowering therapy. LDL cholesterol values are most often calculated as the amount of cholesterol not contained in HDL and VLDL. VLDL is estimated by TG ÷ 5 because the cholesterol concentration in VLDL particles is usually 1/5 of the total lipid in the particle. Thus, LDL cholesterol = TC – [HDL cholesterol + (TGs ÷ 5)] (Friedewald formula). This calculation is valid only when TGs are < 400 mg/dl and patients are fasting, because eating increases TGs. The calculated LDL cholesterol value incorporates measures of all non-HDL, nonchylomicron cholesterol, including that in IDL and lipoprotein (a) [LP (a)]. LDL can also be measured directly using plasma ultracentrifugation, which separates chylomicrons and VLDL fractions from HDL and LDL, and by an immunoassay method. Direct measurement may be useful in some patients with elevated TGs, but these direct measurements are not routinely necessary. The role of apo B testing is under study because values reflect all non-HDL cholesterol (in VLDL, VLDL remnants, IDL, and LDL) and may be more predictive of CAD risk than LDL alone.
b. Other tests: Patients with premature atherosclerotic cardiovascular disease, cardiovascular disease with normal or near-normal lipid levels, or high LDL levels refractory to drug therapy should probably have LP (a) levels measured. LP (a) levels may also be directly measured in patients with borderline high LDL cholesterol levels to establish whether drug therapy is warranted. C-reactive protein and homocysteine measurement may be considered in the same populations.

4.2 Secondary causes: Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid-stimulating hormone (TSH), and urinary protein—should be done in most patients with recently diagnosed dyslipidemia and when a component of the lipid profile has inexplicably changed for the worse.

Screening: A fasting lipid profile (TC, TGs, HDL cholesterol, and calculated LDL cholesterol) should be obtained in all adults ≥ 20 yr and should be repeated every 5 yr. Lipid measurement should be along with assessment of other cardiovascular risk factors, defined as diabetes mellitus, cigarette use, hypertension and family history of CAD in a male 1st-degree relative before age 55 or a female 1st-degree relative before age 65. Indications for screening patients < 20 yr are atherosclerotic risk factors, such as diabetes, hypertension, cigarette smoking, and obesity; premature CAD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dl (> 6.2 mmol/L) or known dyslipidemia in a parent. If information on relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner. Patients with an extensive family history of heart disease should also be screened by measuring LP (a) levels.

5. Treatment: The two major modalities of LDL-lowering therapy are:

a. Therapeutic lifestyle changes (TLC): Lifestyle therapy in clinical management is designated Therapeutic Lifestyle Changes. TLC includes the following: (a) Prospective studies in populations show that dietary patterns modify the baseline CHD risk of populations [237]. In high-risk populations, some of the adverse effects of diet composition undoubtedly relate to established risk factors, e.g., effects of high intakes of saturated fatty acids and cholesterol on LDL cholesterol levels and of high
salt intakes on blood pressure. Moreover, dietary patterns appear to influence baseline risk beyond the known risk factors. For example, populations that consume diets high in fruits, vegetables, whole grains, and unsaturated fatty acids appear to be at a lower baseline risk than can be explained by standard risk factors. The particular nutrients that impart this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients [238]. Therefore, reduced intakes of saturated fats, trans-fat and cholesterol, high intake of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) to decrease serum triglycerides. (b) Therapeutic dietary options to enhance LDL lowering (plant stanols/sterols and increased viscous fiber), (c) increased physical activity and (d) weight control. Because weight reduction can further lower LDL cholesterol and triglycerides and elevate HDL cholesterol levels, maximal improvement in dyslipidemia should be attempted with lifestyle intervention before consideration is given to lipid-lowering drugs [176, 206].

After an appropriate trial of dietary therapy to reduce LDL cholesterol (~ 3 months), two additional therapeutic decisions may be required. First, if the LDL cholesterol goal has not been achieved, consideration may be given to initiating drug therapy. Second, if the metabolic syndrome is present, additional lifestyle changes (i.e., weight reduction and increased physical activity) will be needed. Later, if lifestyle therapies do not alleviate the metabolic syndrome, drug therapy for treatment of the metabolic risk factors may be required [176].
FIG. 4 Atherosclerosis Pathophysiology and Care Management Algorithm

Atherosclerosis

- Smoking
- Obesity
- Hypertension
- Elevated LDL-cholesterol
- Decreased HDL-cholesterol
- Genes
- High saturated fat/cholesterol diet
- Elevated serum triglycerides
- Aging
- Hyperhomocysteinemia
- Inactivity
- Endothelial dysfunction
- Diabetes

Accumulation of plaque
Production of less nitric oxide
Oxidized LDL cholesterol taken up by macrophages
Formation of foam cells and fatty streaks

Clinical Findings
- Elevated serum total cholesterol
- Elevated LDL cholesterol
- Elevated serum triglycerides
- Elevated C-reactive protein
- Low HDL-cholesterol

Nutrition Assessment
- BMI evaluation
- Waist circumference; waist to hip ratio (WHR)
- Dietary assessment for:
  - SFA, trans-fatty acids, omega-3 fatty acids, fiber, sodium, alcohol, and refined carbohydrates

Medical Management
- Bile acid sequestrants
- HMG CoA reductase inhibitors
- Nicotinic acid
- Triglyceride-lowering medication
- Blood pressure—lowering medication
- Medication for glucose management
- Percutaneous coronary intervention (PCI)
  - Balloon
  - Stent
- Coronary artery bypass graft (CABG)

Nutrition Management
- TLC dietary pattern—7% kcal from SFA
- AHA dietary pattern—7% kcal from SFA
- DASH dietary pattern
- Weight reduction if needed
- Increase dietary fiber to 25–30 g/day or more
- Add standls and steroids (2–3 g/day) in multiple doses
- Add omega-3 fats
- Add soy protein
- Add fruits and vegetables for antioxidants
- Reduce dietary cholesterol—<200 mg/day
b. **Drug therapy:** Drug treatment of dyslipidemia is effective and has been demonstrated to reduce long-term cardiovascular risks (Table 9). The first line of therapy in most patients should be a statin agent. However, many patients may suffer from mixed dyslipidemias and require combination pharmacotherapy. The approach to the pharmacological treatment of dyslipidemia should be modified to correct as much of the total dyslipidemia as possible without inducing drug-related side effects [239].

**Table 9. Selected Cholesterol-Lowering Agents Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic/brand names</th>
<th>Benefits</th>
<th>Side effects and cautions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Atorvastatin (Lipitor) 10-80 mg</td>
<td>↓ LDL and triglycerides and moderately increase HDL</td>
<td>Upset stomach, gas, constipation, abdominal pain, cramps, muscle soreness, pain and weakness, increased blood levels of statins with grapefruit juice consumption, drug combinations</td>
</tr>
<tr>
<td>Bile acid-binding resins</td>
<td>Cholestyramine (Questran)</td>
<td>↓ LDLc</td>
<td>Constipation, bloating, nausea, gas, can ↑ triglycerides</td>
</tr>
<tr>
<td></td>
<td>Colesevelam (WelChol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colestipol (Colestid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol absorption inhibitors</td>
<td>Ezetamibe (Zetia) 10 mg</td>
<td>↓ LDLc, mild decreased triglycerides, and mild increased in HDLc</td>
<td>Stomach pain, fatigue</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Fenofibrate (Tricor) 145 mg</td>
<td>Reduce triglycerides and modestly increase HDLc</td>
<td>Gastrointestinal discomfort, increased risk of gallstones, and increased risk of myositis with gemfibrozil combined with statins (contraindicated)</td>
</tr>
<tr>
<td>Niacin (vitamin B3, nicotinic acid)</td>
<td>A variety of prescription or over-the-counter preparations available in 3 forms: immediate release (3-6 grams), timed release (500 mg to 2 grams), and extended release (350-2,000 mg)</td>
<td>↑ HDLc and ↓ LDLc and triglycerides</td>
<td>Flushing of face and neck, nausea, vomiting, diarrhea, gout, high blood sugar, peptic ulcers, GI bleeding</td>
</tr>
</tbody>
</table>

6. **Pathophysiology of Dyslipidemia:** Elevated triglycerides among the Indian population, suggests a role for insulin resistance as the underlying pathophysiology. The atherogenic lipoprotein abnormalities and insulin resistance were demonstrated in another study of only 52 Indian women [240]. A variety of factors may contribute to dyslipidemia among Asian Indians. Asian Indians are generally less physically active and have a diet more rich in carbohydrates and low in polyunsaturated fatty acid, which may contribute to hypertriglyceridemia [241]. Although there is the suggestion
of genetic influences on the atherogenic lipoprotein phenotype, the specific genes involved have yet to be identified. However, one potential candidate is the hepatic lipase gene [242-243]. Hepatic lipase promotes the hydrolysis of phospholipids in intermediate-density lipoprotein and large LDL particles to form smaller, denser LDL particles. It also promotes the conversion of buoyant HDL-2 particles to small, dense, HDL-3 particles by remodeling triglycerides and phospholipids. Therefore, lower hepatic lipase activity is associated with more buoyant, less atherogenic LDL particles. Cohen et al [242] showed that the variation in human hepatic lipase activity can be accounted for by a single haplotype. Homozygosity for the haplotype is associated with low hepatic lipase activity and occurs in 15% of whites and is three times more common in blacks, perhaps explaining why blacks have a less atherogenic lipid pattern than whites. The effect of this gene on the Indian population is not well elucidated. However, a number of other genes have been studied, including apolipoprotein B, apolipoprotein E3, and APOC3 gene polymorphisms. Another important finding is that although obesity is closely linked with the risk of having small-dense LDL and a TG/HDL ratio >3 among whites, this association is markedly less in the Indian population. It has been recognized that although obesity is a contributory factor to insulin resistance and CVD, Asian Indians are not as obese as whites, based on BMI. Still, high body fat, even in the non-obese BMI range, is characteristic of Asian Indians. Data indicate that intra-abdominal visceral fat is more common in Asian Indians compared to other ethnic groups, and this may explain the increased insulin resistance and CVD in this racial group [244]. Accumulation of visceral fat is strongly related to CVD in both obese and nonobese individuals [245]. Mechanistically, an increase in visceral fat leads to increased lipolysis and free fatty acid flux into the liver, where the production of triglyceride-rich very low-density lipoprotein (VLDL) is promoted, causing the formation of small, dense LDL particles [246].

The understanding of the role of dyslipidemia in atherosclerosis has slowly evolved over the past 30 years. From the 7 Countries Study, it was clear that cardiovascular disease mortality was highest in countries that had the highest cholesterol and LDL-C levels and lowest in Greece (Mediterranean) and Asian populations [247]. This focus on cholesterol and LDL-C as a causative factor in
Atherosclerosis has pushed research and clinical trials which have demonstrated significant benefit with cholesterol and LDL-C lowering. In the early understanding, the role of cholesterol was only one of the risk factors considered and documented by the Framingham Studies. It soon became clear that this process was complicated and affected by multiple cardiovascular risk factors including smoking, hypertension, diabetes, age, gender, triglycerides, and high-density lipoprotein cholesterol (HDL-C). This mix of factors when present led to atherosclerotic plaque development. There was a definite interaction when more than one of these risk factors was abnormal. The Framingham risk assessment was constructed using these data and was used in early patient management. Atherosclerosis is a chronic inflammatory disorder in the vessel wall with monocytes (macrophages), T-lymphocytes, proliferation, and migration of smooth muscle cells, production of extracellular matrix, and neovascularization [248].

There has been an explosion of data in the last two decades that has now created a new reality. The cellular and biochemical development of the atherosclerotic plaque has been clearly outlined and illustrated by Dr. Peter Libby [249]. The role of the endothelium (the largest endocrine organ in our body) is central to this process. Normal endothelial function can be altered by traditional risk factor abnormalities. With altered endothelial function a cascade of events occur that cause plaque formation with subsequent inflammation, altered thrombosis, altered vessel tone, and biochemical interactions. Plaque enlargement leads to vascular shear stresses plaque fissure or rupture, platelet adhesion, and vessel thrombosis [250].
FIG. 5 This figure depicts the process of atherosclerosis and the role of inflammation in the progression.

Macrophages became activated in the vessel wall and take in the LDL-C leading to foam cell formation. These macrophages also secrete metalloproteinases that can weaken the plaque cap. They also secrete platelet derived growth factor (PDGF), which induces mitogenesis and promotes plaque neovascularization. Macrophages also elaborate cytokines, which stimulate smooth muscle cell and lymphocyte proliferation with enhanced inflammation. In the presence of plaque and altered endothelial function, there is decreased nitrous oxide production, decreased endothelial-derived relaxation factor, and enhanced platelet activation leading to thromboxane production, which promotes platelet aggregation and vasoconstriction. Platelets also secrete PDGF, which is a potent mitogen (Figures 4 and 5) [251]. This process is further complicated in the presence of lipoprotein (a) elevation and the presence of C-reactive protein stimulated by the ongoing inflammatory process [248]. Cholesterol (LDL cholesterol) is a strong player in the process but not the only one and control of the multiple causes for this inflammatory process is necessary if we are to control this process (Figure 6).
7. **Epidemiology of Dyslipidemia**: Cardiovascular disease is now a principal cause of death by 2020, it will become the leading cause of death and disability worldwide [27]. In developing countries, CVD represents up to 75% of deaths from non-communicable diseases and already accounts for 10% of the developing world’s burden of disability [34]. Dyslipidemia, especially, atherogenic dyslipidemia, has been strongly linked to the pathophysiology of cardiovascular disease [25-26]. Atherogenic dyslipidemia consists of hypertriglyceridemia as well as low HDL cholesterol levels and increased concentration of small-dense LDL particles (LDL pattern B).

In developing countries, the prevalence of the metabolic syndrome varies from 13% in China to 30% in Iran [34]. In an earlier population-based study, the Chennai Urban Population Study in Asian Indians, a significant difference in the prevalence of the metabolic syndrome was found within an urban environment: 19% in the middle income group compared to 7% in the low-income group [30]. In rural areas, prevalence of the syndrome remains significantly lower; people with a traditional lifestyle in rural communities engage in daily physical activity and consume less energy-dense foods [34]. A number of groups have shown that Asian Indians are...
predisposed to metabolic syndrome and insulin resistance, which is often characterized by low HDL cholesterol levels and hypertriglyceridemia [29-30]. Atherogenic dyslipidemia might, therefore, be more prevalent in this racial group compared with whites. Meanwhile, among blacks, reports suggest that the prevalence of atherogenic dyslipidemia may be lesser than among whites [252]. In addition, there are also racial disparities in obesity, an independent risk factor for CVD and atherogenic dyslipidemia [253]. However, Indians, as a group, have a lower prevalence of obesity compared to whites [32], and it is not known what the impact of obesity is upon the prevalence of atherogenic dyslipidemia in blacks or Asian Indians. Several epidemiologic studies have shown that population differences in cardiovascular disease (CVD) exist. CVD is more prevalent among both blacks and Asian Indians than among whites [31, 254-255]. Particularly with regard to Indians, the mortality due to CVD has increased while decreasing among western countries, and this population also has a higher prevalence of premature coronary artery disease [31]. Various studies have revealed that in Asian Indian and black populations, traditional risk factors do not fully explain the increased CVD risk [256-257]. For instance, the prevalence of total cholesterol, LDL cholesterol, and hypertension is lower among Indians than among whites [258]. Therefore, novel risk factors may need to be utilized to identify explanations behind racial differences in CVD. The primary finding of a study was that there were marked racial differences in atherogenic dyslipidemia. The prevalence of small-dense LDL (pattern B) and TG/HDL ratio > 3 is significantly increased among Asian Indians compared to whites in the United States. In contrast, blacks in the United States appear to have a lower prevalence of these atherogenic dyslipidemic patterns compared to whites. These findings are consistent with the findings from several epidemiologic studies suggesting that Indians have increased risk for metabolic syndrome and insulin resistance [29-30].

In the U.K, which has one of the highest mortality rates of CAD, the prevalence of symptomatic CAD in Asian Indians is similar to Whites (8.5% versus 8.2%), but the asymptomatic or silent CAD is higher [259]. In the US, the prevalence of CAD in Asian Indians is 4-fold higher than Whites (10% versus 2.5 %) [32]. The prevalence data underestimate the incidence when case fatality rates are higher.
Therefore, the burden of CAD in Asian Indians is much higher than that reflected by the prevalence data [33].

Cardiovascular diseases are one of the major causes of mortality in Iran [35], and the prevalence of these disorders continues to rise [36]. A study in Iran-Tehran reported an estimated prevalence of >30% in adults [37], which is significantly higher than the prevalence in most developed countries [38]. Iran, as an Eastern Mediterranean country was adopting the Western lifestyle with respect to nutrition habits, smoking and physical inactivity that led to higher prevalence of CVD risk factors among the Iranian community [260]. The age-standardized death rate attributable to cardiovascular diseases and diabetes is estimated to be higher than 400 per 100,000 in Iran. The loss of the Iranian gross domestic product due to heart disease and diabetes in 2015 will be 167% of that in 2006 [261]. A total of 5287 Iranian citizens, aged 15–64 years, were included in a non-communicable diseases survey. The prevalence of hypertriglyceridemia and hypercholesterolemia was 36.4% and 42.9% respectively. The prevalence rates were higher among females (except hypertriglyceridemia) and urban residents [262]. In another study, the prevalence and distribution of high blood pressure, cigarette smoking, dyslipoproteinemia, diabetes mellitus, and obesity was determined in 15,005 subjects, aged three years and over in Tehran urban district-13. In adults, 78 % of men and 80 % of women presented at least one CVD risk factor. The percentage of adult women with two or more risk factors was significantly greater than the one for men. Prevalence of diabetes mellitus, hypertension, obesity, high total cholesterol, low HDL, high triglyceride, and smoking was 9.8, 20.4, 14.4, 19.3, 32, 5.3, and 22.3 %, respectively. In children and adolescents, two or more CVD risk factors were found in 9 % of boys and 7 % of girls [36].
Chapter – III

*Nutrients and Non-Nutrients Influence on Lipidemia*
CHAPTER III

Nutrients and Non-Nutrients Influence on Lipidemia

The ATP-III recommends the therapeutic lifestyle changes (TLC) dietary pattern for primary and secondary prevention of CHD (Table 10). In agreement, the American Heart Association (AHA) recommends diet and lifestyle changes to reduce CVD risk in all people over the age of 2 years [263] (Table 11).

Table 10. Nutrient Composition of the Therapeutic Lifestyle Change Dietary Pattern

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat*</td>
<td>Less than 7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
</tr>
<tr>
<td>Total fat</td>
<td>25%-15% of total calories</td>
</tr>
<tr>
<td>Carbohydrate†</td>
<td>50% to 60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>25-30 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 200 mg/day</td>
</tr>
<tr>
<td>Total calories (energy)§</td>
<td>Balance energy intake and expenditure to maintain</td>
</tr>
<tr>
<td></td>
<td>desirable body weight/prevent weight gain</td>
</tr>
</tbody>
</table>

*Trans- fatty acids are another low-density-lipoprotein raising fat that should be kept at a low intake.
†Carbohydrate should be derived predominantly from foods rich in complex carbohydrates, include grains, especially whole grains, fruits, and vegetables.
§Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/day).
Table. 11 American Heart Association 2006 Diet Recommendation for Cardiovascular Disease Risk Reduction

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight.
- Consume a diet rich in vegetables and fruits
- Choose whole grain, high-fiber foods.
- Consume fish, especially oily fish, at least twice a week.
- Limit intake of saturated fat to <7% of energy, trans-fat to 1% of energy, and cholesterol to <300 mg/day by:
  - Choosing lean meats and vegetable alternatives.
  - Selecting fat-free (skim), 1% fat, and low-fat dairy products.
  - Minimizing intake of partially hydrogenated fats.
  - Minimize your intake of beverages and foods with added sugars.
  - Choose and prepare foods with little or no salt.
  - When consuming alcohol, do so in moderation.
  - When eating food that is prepared outside of the home, follow the American Heart Association Diet and Lifestyle Recommendations.

Dietary Factors

a. Fat: The scientific foundation for the relationship between high intakes of saturated fat and increased LDL levels dates back several decades. The major LDL-raising dietary constituents are saturated fat and cholesterol. A reduction in intakes of these components is the core of the TLC Diet.

The rationale for the recommendations for each component of the TLC diet will be described briefly.

1) Saturated fatty acids: Saturated fatty acids are a major dietary determinant of LDL cholesterol level [221]. The effects of saturated fatty acids on serum total cholesterol (and LDL cholesterol) levels have been studied extensively [264]. Several meta-analyses and reviews have been carried out to estimate the impact of saturated fatty acids on cholesterol levels [265-266]. These analyses indicate that
for every 1 percent increase in calories from saturated fatty acids as a percent of total energy, the serum LDL cholesterol rises about 2 percent. Conversely, a 1 percent reduction in saturated fatty acids will reduce serum cholesterol by about 2 percent. The most hypercholesterolemic-promoting or atherogenic SFAs in order of potency are myristic (C14:0), palmitic (C16:0), and lauric (C12:0) acids [267]. Most dietary palmitate comes from animal foods. Myristic acid is found mostly in butterfat and coconut and palm kernel oils. It is less prevalent in the American diet than palmitic acid. Lauric acid, the only medium-chain SFA, is also found in palm kernel and coconut oils. Of all the added fats in the diet, the most hypercholesterolemic promoting are palm kernel, coconut, and palm oils; lard; and butter [268]. SFAs raise serum LDL cholesterol by decreasing LDL receptor synthesis and activity [268].

2) Trans fatty acid: Trans fatty acids are those in which double bonds are in the trans configuration. They are generally produced by hydrogenation of vegetable oils but some are found naturally in animal fats. Substantial evidence from randomized clinical trials indicates that trans fatty acids raise LDL cholesterol levels, compared with unsaturated fatty acids [269-271]. These studies also show that when trans fatty acids are substituted for saturated fatty acids, HDL cholesterol levels are lower [272], with a dose response effect observed.

Evidence from some epidemiological cohort studies suggests that high intakes of trans fatty acids are associated with higher risk for CHD [272-274]. Whether this association is due to adverse effects of trans fatty acids on lipoproteins, to other adverse actions, or to confounding variables is uncertain.

Major sources of trans fatty acids in the diet include products made from partially hydrogenated oils such as baked products including crackers, cookies, doughnuts, breads, and products like french fries or chicken fried in hydrogenated shortening. Animal sources including dairy products provide smaller amounts of trans fatty acids. Soft margarines, tub and liquid, and vegetable oil spreads have low amounts of trans fatty acids. Some margarines and spreads are now trans-fatty acid free. Some hydrogenation of vegetable oils is the primary technology
currently used to provide form to food products, so that they can be eaten out of the hand, rather than with a spoon [275-277].

3) **Monounsaturated fatty acids:** The most common form of monounsaturated fatty acids is oleic acid, which occurs in the cis form. Substitution of cis-monounsaturated fatty acids for saturated fatty acids results in a fall in LDL cholesterol levels [266]. Monounsaturated fatty acids as part of a diet that is low in saturated fatty acids and cholesterol and rich in vegetables, fruits, and grain products have received increased attention as being potentially valuable for risk reduction due to their association with low rates of CHD in olive oil consuming populations of the Mediterranean basin [278-279].

The AHA does not have any recommendation for the cis form of MUFAs [280]. Oleic acid (C18:1) is the most prevalent MUFA in the American diet. Substituting oleic acid for carbohydrate has almost no appreciable effect on blood lipids; however, replacing SFAs with MUFA (as would happen when substituting olive oil for butter in a diet) lowers serum cholesterol levels, LDL cholesterol levels, and triglyceride levels to about the same extent as PUFAs. The effects of MUFAs on HDL cholesterol depend on the total fat content of the diet [281]. In epidemiologic studies high-fat diets of people in Mediterranean countries have been associated with low blood cholesterol levels and CHD incidence [280]. Among other factors, the main fat source is olive oil, which is high in MUFA. This observation led to many studies on the benefits of high-fat and high MUFA diets. More recently a Mediterranean type step I diet was shown to decrease recurrent CVD by 50% to 70% [282]. This diet emphasizes fruits, root vegetables (carrots, turnips, potatoes, onions, radishes), leafy green vegetables, breads and cereals, fish, foods high in α-linolenic acid (flax, canola oil), vegetable oil products (salad dressing and other products made with nonhydrogenated oils), and nuts and seeds (walnuts and flaxseed) [283].

4) **Polyunsaturated fatty acid:** Polyunsaturated fatty acids, consisting mainly of n-6 linoleic acid, reduce LDL cholesterol levels when substituted for saturated fatty acids. At high intakes, linoleic acid also can produce small reductions in HDL cholesterol and triglycerides, although these responses are variable. Compared to
cis-monounsaturated fatty acids, polyunsaturated fatty acids often cause a slightly greater reduction in LDL cholesterol levels [266]. Several controlled clinical trials have compared the effects of polyunsaturated fatty acids, as a replacement for saturated fatty acids, on coronary endpoints. Meta-analysis of trial results indicates that substitution of polyunsaturated fatty acids for saturated fatty acids reduces risk for CHD [284]. This positive result is supported by research in primates that indicates that polyunsaturated fatty acids are antiatherogenic when substituted for saturated fatty acids [285]. Studies suggest that high intakes of n-6 PUFAs may exert adverse effects on the function of vascular endothelium or stimulate production of proinflammatory cytokines. A low ratio of omega-6: omega-3 PUFA is recommended [286].

Omega-3 fatty acid: The main omega-3 fatty acids, i.e., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are high in fish oils, fish oil capsules, and ocean fish. Many studies have shown that eating fish is associated with a decreased CVD risk. The recommendation for the general population for fish consumption is to eat fish high in omega-3 fatty acids (salmon, tuna, mackerel, sardines) at least twice a week [287]. For patients who have CVD, 1 g of EPA and DHA combined is recommended from fish if possible but, if not, then from supplements. Patients who have hypertriglyceridemia need 2 to 4 g of EPA and DHA per day for effective lowering [288]. Omega-3 fatty acids lower triglyceride levels by inhibiting VLDL and apo B-100 synthesis and by decreasing postprandial lipemia [281].

5) Dietary cholesterol: Dietary cholesterol causes marked hypercholesterolemia in many laboratory animals, including nonhuman primates. High intakes of cholesterol in humans, however, do not cause such a marked increase in serum cholesterol. However, controlled metabolic studies in humans show that high cholesterol intakes raise LDL cholesterol levels. The degree of rise varies from person to person, as is true for all nutrients. Meta-analyses of studies done in controlled settings confirm the LDL-raising action of dietary cholesterol [289-290]. A recent meta-analysis showed that dietary cholesterol raises the ratio of total to HDL cholesterol, adversely affecting the serum cholesterol profile [291].
A lesser effect of dietary cholesterol has been found in studies carried out in the outpatient setting [292] in this condition, failure to detect the full effect of dietary cholesterol is likely related to lack of tight metabolic control. On average, the response of serum cholesterol to dietary cholesterol as revealed in tightly controlled studies is approximately 10 mg/dl per 100 mg dietary cholesterol per 1000 kcal [293]. In the past 40 years, there has been a progressive decline in intakes of dietary cholesterol. This has been the result of decreased intakes of eggs, high-fat meat, and high-fat dairy products. This reduction in cholesterol intake, along with a substantial reduction in the proportion of calories from saturated fatty acids, corresponds with the decline in serum cholesterol levels that has occurred in the U.S. population over four decades [294]. At present, the average U.S. daily consumption of cholesterol is 256 mg, higher for men (331 mg) than for women (213 mg). Eggs contribute about one-third of the cholesterol in the food supply and this fraction has increased somewhat in recent years [295]. Other sources of dietary cholesterol include animal products, dairy, meats, poultry, and shellfish [281].

b. Carbohydrate: When carbohydrates are substituted for saturated fatty acids, the reduce in LDL cholesterol levels equals that with monounsaturated fatty acids. However, compared with monounsaturated fatty acids, substitution of carbohydrate for saturated fatty acids frequently causes a fall in HDL cholesterol and a rise in triglyceride [266, 296]. This effect apparently persists in the long term, as suggested by differences in population lipid levels in the presence of different habitual diets [297-298]. When carbohydrate is consumed along with high-fiber diets, however, the rise in triglycerides or fall in HDL cholesterol has been reported to be reduced [299].

With the AHA dietary patterns' emphasis on fruits, vegetables, legumes, and whole grains, there would be adequate fiber to lower LDL cholesterol. Particularly, the soluble fibers in pectins, gums, mucilages, algal polysaccharides, and some hemicelluloses lower LDL cholesterol. The quantity of fiber needed to produce the lipid lowering effect varies by food source; higher quantities of legumes are needed than of pectin or gums. Proposed mechanisms for the
The hypocholesterolemic effect of soluble fiber include the following: (1) the fiber binds bile acids, which lowers serum cholesterol as it repletes the bile acid pool; and (2) bacteria in the colon ferment the fiber to produce acetate, propionate and butyrate, which inhibit cholesterol synthesis. The role of fiber, if any, on inflammatory pathways is not well established [300]. Insoluble fibers such as cellulose and lignin have no effect on serum cholesterol levels. Of the total recommended fiber intake (25 to 30 g daily for adults), approximately 6 to 10 g should be from soluble fiber. This level is easy to achieve with the recommended five or more servings of fruits or vegetables per day and six or more servings of grains (if whole grains and high-fiber cereals are chosen) [281].

c. **Protein:** Generally, dietary protein has little effect on serum LDL cholesterol level or other lipoprotein fractions. However, substituting soy protein for animal protein has been reported to lower LDL cholesterol [301]. Plant sources of protein are predominantly legumes, dry beans, nuts, and, to a lesser extent, grain products and vegetables, which are low in saturated fats and cholesterol. Animal sources of protein that are lower in saturated fat and cholesterol include fat-free and low-fat dairy products, egg whites, fish, skinless poultry, and lean meats [302]. Only very large intakes of soy protein (at least half of a person's daily protein intake) may decrease LDL cholesterol by a few percent when it replaces animal protein. Using soy foods such as tofu, soy butter or soy nuts may have benefits for cardiovascular health in that they contain other protective nutrients such as PUFA and fiber [281].

d. **Antioxidants:** Oxidative stress is a putative cause of atherosclerotic disease. In experimental studies, oxidation of LDL is a critical step in the development and progression of CHD. Thus, a large body of research has been directed towards the potential of antioxidants for reducing CHD risk. Antioxidants under investigation include alpha-tocopherol (vitamin E), ascorbic acid (vitamin C), beta-carotene, ubiquinone (coenzyme Q10), bioflavonoids, and selenium [302].

1) **Vitamin E:** Vitamin C is the predominant plasma antioxidant. Vitamin E is the most concentrated antioxidant carried on LDLs, the amount being 20 to 300 times greater than any other antioxidant. A major function of vitamin E is to prevent
oxidation of PUFA in the cell membrane. Epidemiologic studies suggest that vitamin E and carotenoids are inversely related to CVD. [288]. Findings support the hypothesis that supplemental vitamin E may reduce the risk of coronary disease [303]. However, RRR-a-tocopherol, the natural form of vitamin E, shows promise as an anti inflammatory agent [286], [304]. Results of a study suggest that in postmenopausal women the intake of vitamin E from food was inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements [305]. In a study of more than 121,000 female nurses between the ages of 30 and 55 years, food frequency questionnaires assessed daily intake of dietary and supplemental vitamins E, C and β-carotene. Women in the highest quintile of vitamin E intake (about 200 IU per day) had a 34 percent lower CHD risk than women in the lowest quintile (less than 3 IU per day). Risk reduction was noted with a daily intake of greater than 100 IU of vitamin E but not with daily use of multivitamins, vitamin C supplements or β-carotene supplements [306].

2) Ascorbic Acid: Evidence from ecological studies links low intake of vitamin C with increased rates of cardiovascular disease. This water-soluble vitamin scavenges plasma free radicals and prevents their entry into LDL particles [307]. Vitamin C regenerates active vitamin E and enhances cholesterol excretion. Vitamin C improves endothelium-dependent vasodilation and reduces monocyte adhesion [308-309]. Supplementation with vitamin C (1,000 mg) and vitamin E (800 IU) before the ingestion of a high-fat meal has been found to reverse endothelial dysfunction and vasoconstriction following the meal [310]. In Britain, for example, rates of stroke and coronary heart disease are highest in regions where consumption of fruit and vegetables is lowest [311-312]. However, studies that examined the association of vitamin C and cardiovascular disease show conflicting results [313-314]. In prospective studies of a Dutch population [315] and in Swedish study [316] of women no relation was found between vitamin C and coronary mortality. Numerous studies examined the effect of vitamin C independent of vitamin E [303, 306, 317].
3) **Beta Carotene:** Observational epidemiologic studies suggest that people who consume more fruits and vegetables containing beta carotene have somewhat lower risks of cancer and cardiovascular disease, and earlier basic research suggested possible mechanisms. In contrast, the intake of vitamins A and C was not related to lower risks of dying from coronary disease. In a study the observations with regard to vitamins A and C were similarly not definitive, but they suggest that increased intake of these vitamins is not likely to lower the risk of death from coronary heart disease [305]. Research supports the benefit of a carotenoid-rich diet, but not β-carotene supplementation. The Beta-Carotene and Retinol Efficacy Trial [318] combined β carotene and retinol supplementation in 18,314 smokers and patients with asbestos exposure. However, the study was terminated prematurely because of a significant increase in lung cancer mortality and a nonsignificant increase in CHD mortality. In 12 years of β-carotene supplementation in 22,071 male physicians, no significant beneficial effects on CHD mortality, nonfatal MI or stroke were found [319].

4) **Ubiquinone (coenzyme Q 10, CoQ10):** Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like substance found in the inner mitochondrial membrane. It is normally involved in a series of enzymatically catalyzed sequential reactions necessary to carry out oxidative phosphorylation through the electron transport chain which is an essential process that provide energy to vital organs such as the brain, heart, muscles and kidneys [320]. Ubiquinone may reduce symptoms and improve ejection fractions in patients with heart failure [321-322]. Coenzyme Q10 is a vital adjuvant therapy for patients with congestive heart failure (CHF), even when traditional medical therapy is successful. Adjunctive therapy with Q10 may allow for a decreasing of other pharmacological therapies, improvement in quality of life, and a reduction in the incidence of cardiac complications in congestive heart failure [321].

5) **Bioflavonoids:** The antioxidant activities of bioflavonoids have been shown to reduce risk factors associated with cardiovascular disease [323]. Populations that consume a high level of these foods have reduced incidence of cardiovascular mortality and morbidity [324].
A growing body of evidence indicates that bioflavonoids from tea maintain levels of antioxidant capabilities in the plasma that exert beneficial effects on the cardiovascular system. It has also been shown that the antioxidant capabilities of bioflavonoids act in a number of ways to restore vasculature integrity and inhibit atherogenesis [324].

6) **Selenium:** Selenium is a potent antioxidant regulating the activity of the glutathione peroxidase enzymes, which catalyse the detoxification of hydrogen peroxide and organic hydroperoxides. Selenium deficiency has been associated in the aetiopathogeny of Keshan disease, an endemic cardiomyopathy observed in China, and in other cases of congestive cardiomyopathy in subjects on artificial nutrition. However, the evidence from case-control and prospective studies for an relationship between low selenium status and cardiovascular diseases remains controversial. Mechanisms whereby selenium protects against such diseases include increased resistance of low-density lipoproteins against oxidative modification, modulation of prostaglandin synthesis and platelet aggregation, and protection against toxic heavy metals. The therapeutic advantage of selenium administration in the prevention and treatment of cardiovascular diseases still remains insufficiently documented [325].

Due to the increased risk of diabetes and cardiovascular disease in people with the metabolic syndrome, there is an urgent need for strategies to prevent the emerging global epidemic of this condition. Therefore, determination of reason of dyslipidemia, evaluation of the individual patient’s health and risk status, focus on treatment goals and a clear understanding of the mechanism and effects of lipid lowering agents are crucial. The primary management goals of the metabolic syndrome are to reduce the risks of cardiovascular disease and diabetes. Although LDL levels are considered as the primary goal in the management of dyslipidemia, evidence recommends that HDL and triglyceride levels are also associated with coronary risk and should not be ignored. If desired levels cannot be reached with monotherapy, then combination therapy should be considered. Lifestyle modifications, including regular physical activity, food habits and even modest weight loss, could reduce the prevalence of the syndrome. Thus, community-wide efforts to change health behaviors are vital to decrease the death and disability resulting from the metabolic syndrome in developing countries.