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Review

Roles of dietary lipids in nutrition-medicine

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The objective of this study is to investigate the importance of dietary lipids-related diseases with a view to exploring feasible preventive and curative dietary and/or drug therapies. Foods low in cholesterol and saturated fatty acids content but moderate in poly unsaturated fatty acids (PUFA), including chicken, lean fish meal, and plant seeds rich in phytosterols (e.g β-sitosterol), such as soya bean , corn and groundnut, seeds, should form the chief of the dietary protein sources for people predisposed or vulnerable to atherosclerosis, cardiovascular diseases and obesity. Large dietary intake of linoleic fatty acids should be avoided by those susceptible to high blood pressure caused by the over-expression of prostaglandin endoperoxidase synthase. Drugs that inhibit prostaglandin endoperoxidase synthase (a cyclooxygenase, COX) would reduce prostaglandin synthesis in normal individuals (individuals not associated with over-expression of COX) causing hypo-prostaglandinosis which increases the risk of cardiovascular incidences such as heart attack and strokes. Over-expression of COX-2 can be controlled by such drugs as inhibit COX (e.g ibuprofen vasoprin, and aspirin), by which means heart attacks, cardiac arrests, and strokes are prevented in patients suffering from hyper-prostaglandinosis.

Key words: Phytosterol, atherosclerosis, prostaglandin endoperoxidase synthase, cardiovascular.

INTRODUCTION

Lipids are oily and greasy organic substances that are water insoluble and occur naturally in cells and tissues of living organisms from where they are extractable by organic solvents such as chloroform and ether. Lipids are a group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids and others. The biological functions of lipids include energy storage (Fahy *et al.,* 2009). Lipids also function in signaling and acting as structural components of cell membranes (Subramaniam *et al.,* 2011). Lipids are used in the manufacture of cosmetics and packaged food as well as in nanotechnology (Mashaghi *et al.,* 2013). Dietary lipids are lipids obtained from foods. Lipids in the form of triacylglycerols are a source of chemical energy, essential fatty acids, and non-essential fatty acids, in living organisms. The major dietary lipids for humans and other animals are animal and plant triglycerides, sterols, and membrane phospholipids (Russo, 2009). Lipid metabolism is essential to the synthesis and bio-degradation of the lipid stores (e.g. adipocytes) and produces the structural and functional lipids characteristic of individual tissues. Nutrition-Medicine is a branch of medicine in which the uses of foods/diets/nutrients are used in the prevention and/or treatment of specific maladies or diseases is explored. In Nutrition-Medicine, investigations are made to elucidate the effects of the metabolism of nutrients obtained from dietary sources on certain disease conditions. The objective of this study is to investigate the importance of dietary lipids in the prevention and cure of nutrition-related diseases. In severe diabetes mellitus due to failure of insulin secretion or action, patients fail to synthesize fatty acids and triacylglycerols from carbohydrates or amino acids but rather show increased rates of fat oxidation and ketone body formation (Gerich *et al*., 2001). Invariably, low dietary intake of essential fatty acids is prescribed as part of dietary therapy for diabetics, in order to forestall the unwanted consequences of acidosis.

Nutrition-related diseases and dietary therapies

People with intestinal and/or pancreatic diseases in which there are defective lipid absorption, failure to absorb, with any degree of efficiency, the dietary fat soluble vitamins (A, D, E, and K), resulting in the deficiency of fat soluble

vitamins. The deficiency can be overcome by increasing the amount of fat-soluble vitamins orally administered to the patient or in extreme cases by administering the fat-soluble vitamins via intra-muscular or intra-venous routes (Murray *et al.,* 2009a).Essential fatty acids include linoleic (an omega-6 fatty acid), and α-linolenic acids (an omega-3 fatty acid). Experimental animals and humans are unable to synthesize essential fatty acids and must obtain the same from dietary sources. Essential fatty acids are abundant in plant foods (safflower, sunflower, and corn oils; green leaves of plants flax, rapeseed, walnut, and soy (Russo, 2009), but occur in much lower amounts in meat and dairy products. Cholesterol, a class of fats, known as sterols, produced by animals is present in significant amounts in egg yolk, butterfat, and meat but absent from plant foods. Plants produce the phyto analogues or derivatives of sterols, known as phytosterols e.g β-sitosterol and stigmasterol (Murray *et al.,* 2009b).Atherosclerosis is a disease condition arising from hypercholesterolemia (elevated levels of plasma cholesterol). Atherosclerosis is the formation of thick deposits of cholesterol, and its ester derivatives, in the inner surfaces of blood vessels causing local anoxia. Atherosclerosis predisposes to strokes and coronary infarction. Animal fats contain two components that predispose to atherosclerosis, and are saturated fatty acids which constitute the chief of non-essential fatty acids and cholesterol (Truswell, 1994). It is a well-established fact that consumption of trans fats, such as those present in partially hydrogenated vegetable oils, conduce to cardiovascular disease [Mozaffarian and Willett (2007); Micha and Mozaffarian (2008); Dalainas and Ioannou (2008)]. n-3 essential fatty acids (EFAs) arrest cell proliferation in several tumor models (Actis *et al*., 2002).Most animal fats, especially, those from meat, milk, and eggs have low content of essential fatty acids e.g. polyunsaturated fatty acids (PUFA). Two exceptions are chicken and fish lipids, which are relatively rich in PUFA but low in cholesterol content. Plant lipids on the other hand, are very rich in essential fatty acids, PUFA and phytosterols. Lipid molecules are tightly bound to specific proteins by means of non-covalent linkages, to form lipoproteins. Lipoproteins found in the plasma are known as plasma lipoproteins. Specific plasma lipoproteins contain polar lipids, triacylglycerols, cholesterol and cholesterol esters. The combination of high plasma level of low density lipoproteins (LDL), and a low plasma level of high density lipoproteins (HDL), is an important causative factor of atherosclerosis. Consumption of diets rich in saturated animal fats but low in PUFA content tends to decrease the concentration of high density lipoproteins, and increase the concentration of low density lipoproteins, and total cholesterols in the blood. Consumption of diets moderate in PUFA and phytosterols but low in saturated animal fats and cholesterol content, tends to increase the concentration of high density lipoproteins and decreases the concentration of low density lipoproteins, and total cholesterols in the blood, thus conducing to good health [Denke (2006); Murray *et al.,*(2009b)].Replacing 60% of saturated fats by other fats and avoiding 60% of dietary cholesterol would reduce blood total cholesterol by about 0.8 mmol/l (Clarke *et al*., 1997). There is significant statistical correlation between the incidence of cardiovascular diseases and low levels of high density plasma lipoproteins, and high levels of low density plasma lipoproteins and total cholesterol (Carmena *et al*., 2004). A consistent inverse relation of high-density lipoprotein cholesterol (HDLC) levels and coronary heart disease event rates was apparent in a British Regional Heart Study (BRHS) of 1986 as well as in the four American studies viz: Framingham Heart Study (FHS), Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCF), Coronary Primary Prevention Trial (CPPT), and Multiple Risk Factor Intervention Trial (MRFIT) (Gordon *et al*., 1989). The survivors of myocardial infarction, assigned to a Mediterranean α-linolenic acid rich diet, had a markedly reduced rate of recurrence, other cardiac events and overall mortality (De Lorgeri *et al*., 1994). In view of these findings, foods low in cholesterol, and saturated fatty acids content, but moderate in PUFA, including chicken, lean fish meal, obtained from salmon, herring, e.t.c., and plant seeds rich in phytosterols such as soya bean, corn, and groundnut, should form the chief of the dietary protein sources for people predisposed or vulnerable to cardiovascular diseases and obesity. Lean meat (defattened meat) and skimmed milk (defattened milk), complement these dietary protein sources. The term 'lean fish', has been used to distinguish between the preferred processed fish type, and some cartilaginous fishes that contain blubbers of fatty tissues. Obesity which increases the risk of cardiovascular diseases, hypertension and diabetes, is partly caused by high caloric intake, sourced from fats, carbohydrates, and proteins, in excess of body needs but is also associated with a strong, hereditary, genetic factor. Calories consumed as ethanol in excess of the daily caloric requirement, are converted into fats (saturated fatty acids and cholesterol), which conduce to obesity, and atherosclerosis. Linoleic acid may be linked to obesity by promoting over-eating and damaging the arcuate nucleus in the brain's hypothalamus (Raloff, 2012). Reduced dietary intake of linoleic acid would control obesity and conduce to good health.Glucagon-like peptide-1 (GLP-1) reduces gastric emptying, increases satiety and can result in weight loss. lipid activators of GLP-1 release are lipid compounds which are capable of activating G-protein coupled receptor 119 and which thereby stimulate GLP-1 release. These lipid compounds are useful in the prophylaxis and/or treatment of metabolic disorders and complications thereof, such as, type 2 diabetes mellitus (T2DM), obesity, insulin resistance, and cardiovascular disease. Lipids such as lysophosphatidylcholine and oleoylethanolamide (OEA),

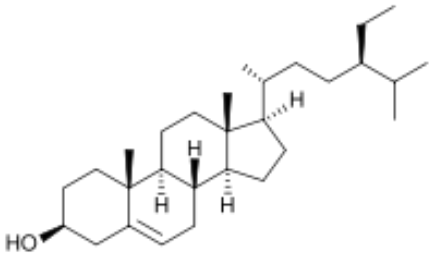

Figure 1. The Chemical Structure of β-sitosterol.

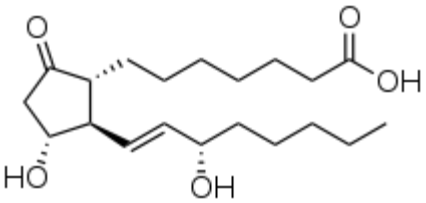

Figure 2. Chemical Structure of Prostaglandin E_1 (Alprostadil).

have been identified as potent agonists of GPR119 (Ahrén, 2009).The administration of plant sterols (especially, β-sitosterol, shown in Figure 1), a phytosterol synthesized by plants, to people suffering from hypercholesterolemia, lowers the plasma low density lipid (LDL) cholesterol and decreases the risk of atherosclerosis, coronary heart diseases, and stroke (Hansel *et al*., 2007). Addition of β-sitosterol to low doses of soy protein seems to be a practical and safe alternative for patients seeking modest reductions in low density lipoprotein cholesterol (LDL-C) (Cicero et al., 2002). β -sitosterol, a structural analogue of cholesterol, mimics the regulatory actions of cholesterol thus inhibiting the metabolism of cholesterol to a large extent by inhibiting the absorption of cholesterol in the intestine (Matsuoka *et al*., 2008). The IUPAC name of β-sitosterol is 17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol.Tre-en-en is a food supplement produced by GNLD® International and is prepared with a variety of phytosterols and PUFA such as omega-3-fatty acids and omega-6-fatty acids. Tre-en-en is essentially effective in the treatment of hypercholesterolemia. The dietary protein quality of egg which contains all the essential amino acids in good proportions but also cholesterol could be improved by a dietary intake of a combination of eggs and plant oils, rich in phytosterols. Patients suffering from hypocholesterolemia should eat sparingly of food rich in phytosterols, especially, foods rich in β-sitosterol but more of moderate cholesterol-containing foods. There is a strong genetic factor associated with incidences of coronary artery diseases which is influenced by smoking, drinking, alcoholism, hypertension and obesity. Atherosclerosis is therefore a disease of complex origin, influenced by a variety of factors (Higgins, 2000).

Stigmasterol is a phytosterol that prevents stiffening of joints. The lipid, ergosterol is a yeast sterol, which upon irradiation by ultraviolet rays is converted to ergocalciferol or vitamin D_2. Concurrent administration of ergocalciferol and calcium is effective against rickets in children and osteomalacia in human adults. The recommended daily allowance of vitamin D is 10µg. Vitamin E, also known as tocopherol, protects membrane lipids against oxidative destruction of polyunsaturated fatty acids (PUFA), and facilitates regeneration of liver and altered membrane functions. The recommended daily allowance of vitamin E is 10mg. Vitamin E occurs naturally in vegetable oils and wheat germ. Protein energy malnutrition (PEM) is characterized by significantly low levels of plasma lipids and cholesterol (González *et al*., 1992). Plant oils, rather than carbohydrates sources are used as main energy supply, in therapeutic diets that engender rapid catch-up growth rates during alleviation of PEM in patients. The activity of the enzyme delta 6-desaturase is deficient (below normal) in patients suffering from the inheritable, autosomal disease known as Darier's disease (Oxholm *et al*., 1990). The administration of the main dietary essential fatty acids, linoleic acid and alpha-linolenic acid, to patients of Darier's disease, should be minimal. Epidemiologic and experimental studies on the aetiology of cancer have implicated dietary lipids as causative agents of cancer, especially, breast, colon-rectal, and prostate cancers. Cancer is one of the main causes of worldwide mortality and morbidity. Fish oil, rich in polyunsaturated fatty acids of the n-3 serie, as well as olive oil, rich in monounsaturated fatty acids-primarily oleic acid, have inhibitory effects on tumor formation (Escrich *et al*., 2007). Conversely,high intake of n-6. Serie of polyunsaturated fatty acids and saturated fats have tumor-enhancing effects. Significant reduction in cancer, owed to the dietary intake of lipids has been associated with the oral administration of nutritional supplements of polyunsaturated n-3 fatty acids and other components such as arginine, RNA, and lysine (Granados *et al*., 2006).Prostaglandins are a class of eicosanoids fatty acid derivatives or lipid–soluble organic acids containing 5-carbon ring, and are derived from the precursor essential fatty acids, linoleic acid, and γ-linolenic acid, via the unsaturated fatty acid, arachidonic acid. Prostaglandins are regulators of hormone action and are hormone-like substances that regulate many different cell functions. The various forms of prostaglandins include prostaglandins G_1, G_2, E_1, E_2, $F_{2\alpha}$, and GH_2. The chemical structure of prostaglandin E_1 is shown in Figure 2. Prostaglandins are responsible for producing/increasing perception of fever, and inflammation and its associated pain (Nelson and Cox, 2008). A decrease in omega-6 fatty acids has been shown to attenuate inflammation due to reduced production of prostaglandins (Kinsella *et al*., 1990).

Table 1 . Types, Receptors, and Functions of Prostaglandins

Type	Receptor	Function
PGI_2	IP	vaso-dilation inhibit platelet aggregation bronchodilation
	EP_1	broncho-constriction GI tract smooth muscle contraction
	EP_2	broncho-dilation GI tract smooth muscle relaxation vaso-dilation
PGE_2	EP_3	gastric acid secretion gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction lipolysis inhibition autonomic neurotransmitters platelet response to their agonists and atherothrombosis in vivo
$PGF_{2\alpha}$	FP	uterus contraction broncho-constriction

(Fabre *et al*., 2001; Gross *et al*., 2007).

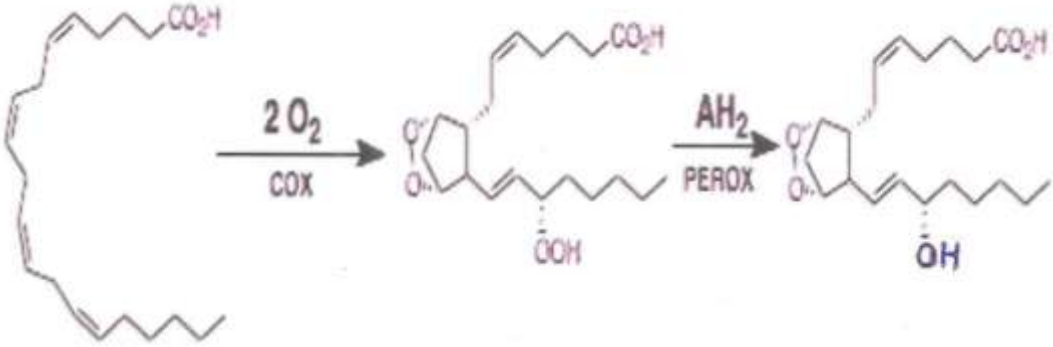

Figure 3. Activity of prostaglandin endoperoxide synthase in the biosynthesis of PGG_2 and PGH_2.

Contrary to the latter finding, Poudel-Tandukar *et al*., (2009), posited that increased intake of not only alpha-linolenic acid (n-3 PUFA), but also linoleic acid (n-6 PUFA), has a beneficial effect on systemic inflammation in men. The variation in findings could be a function of differences in the level of expression of prostaglandin endoperoxidase synthase (a cyclooxygenase, COX), in the individuals, tested. Excessive production of prostaglandins has also been implicated as a causative factor of high blood pressure and cardiovascular incidences. For these reasons, dietary intake of large amounts of linoleic fatty acid should be avoided by those susceptible to high blood pressure. There are ten known prostaglandin receptors on various cell types. The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of functions, some of which are shown in Table 1. Cyclooxygenase-2 (COX-2) inhibition would reduce prostaglandin-E2 levels (COX enzymes perform the first step in the production of prostaglandins) , it might increase macrophage apoptosis and promote plaque rupture. macrophage cell death promotes plaque rupture, causing heart attacks and strokes (Moreno, 2010). Drugs that inhibit prostaglandin endoperoxidase synthase (a cyclooxygenase, COX) would reduce prostaglandin synthesis in normal individuals (individuals not associated with over-expression of COX) causing hypo-prostaglandinosis which increases the risk of cardiovascular incidences such as heart attack and strokes. Three main factors have been implicated as causative agents of over-expression of COX, leading to increased levels (hyper-prostaglandinosis).These factors are: age (some older individuals are susceptible to over-expression of COX);for reason of genetic constitution, some individuals are more

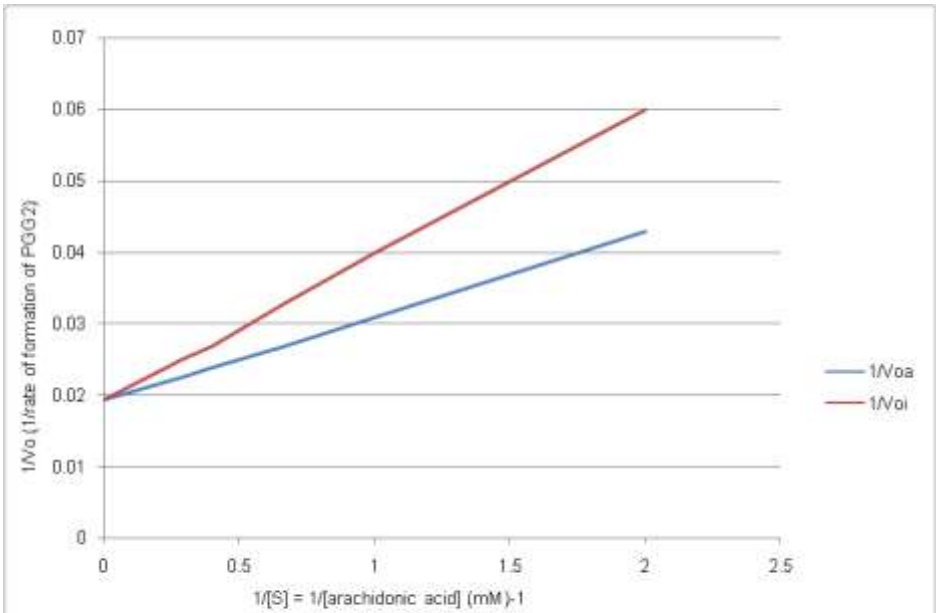

Figure 4. The Lineweaver-Burk plots/Double reciprocal plots of the of the inhibited and uninhibited prostaglandin endoperoxide synthase enzyme-catalyzed reactions

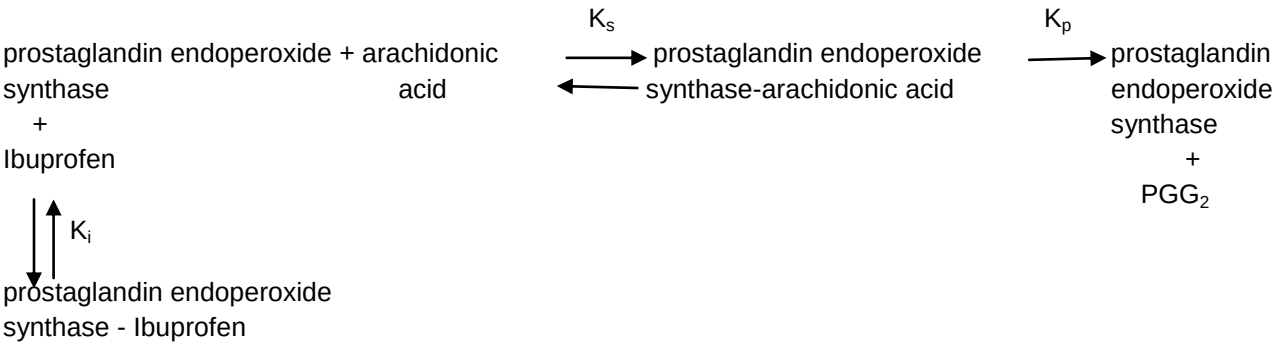

Figure 5. The equilibria of the prostaglandin endoperoxide synthase enzyme-catalyzed reaction.

susceptible to over-expression of COX than others; and antigenic/ toxic factors or diseases could evoke the over-expression of COX in individuals. Patients with carotid atherosclerosis depict an over-expression of COX-2 in the peripheral blood mononuclear cells (PBMC) as well as in the vulnerable region of plaques (Gómez-Hernández *et al*., 2006). Patients suffering from over-expression of COX are thus prone to heart attacks and strokes.Over-expression of COX-2 can be controlled by drugs that inhibit COX, by which means heart attacks, cardiac arrests, and strokes are prevented in patients suffering from hyper-prostaglandinosis. The enzyme, prostaglandin endoperoxide synthase, expresses a cyclooxygenase activity, in using oxygen to convert arachidonic acid to prostaglandin G_2 (PGG_2), but expresses a peroxidase activity in converting PGG_2 to prostaglandin H_2 (PGH_2), in the presence of a reducing agent, as shown in Figure 3. Both the peroxidase and the cyclooxygenase activities are inactivated during catalysis by mechanism-based, first-order processes. This means that the peroxidase or cyclooxygenase activities fall to zero within 1–2 minutes, even in the presence of sufficient substrates [Garavito *et al*., (1996), So and Swinney (1996), Wu *et al*.,(1999)] .Thromboxanes are derived by biosynthesis from prostaglandin precursors and function to induce constriction of blood vessels, platelet aggregation, and early steps in blood clotting. Regular administration of low doses of aspirin, reduce the problem of heart attacks and strokes by reducing thromboxane production (Nelson and Cox, 2008a). Aspirin, vasoprin and Ibuprofen are drugs which function as inhibitors of prostaglandin endoperoxide synthase

(cyclooxygenase, COX) and thus reduce the biosynthesis of PGG_2 by which means inflammation, pains and risk of heart attacks and strokes are significantly reduced in individuals characterized with over-expression of COX. Natural inhibitors of COX include: fish oils, flavonoids and vitamin D (O'Leary *et al*., 2004; Moreno *et al*., 2006). Moreover, imbalance between cyclooxygenase-2 (COX-2) and cytochrome P450 (CYP450) arachidonic acid metabolizing enzymes in the kidney may contribute to the renal damage associated with obesity (Imig *et al*., 2005). For this reason, over-consumption of dietary fatty acids precursors of arachidonic acid may lead to obesity. The Lineweaver-Burk plot/Double reciprocal plot of the uninhibited prostaglandin endoperoxide synthase enzyme catalyzed reaction in which arachidonic acid is converted to PGG_2 is shown in Figure 4, and the straight line equation is given as

$$\frac{1}{V_{oa}} = \frac{K_M}{V_{max}}\frac{1}{[S]} + \frac{1}{V_{max}} = 0.011695906\frac{1}{[S]} + \frac{1}{51.546}$$

V_{oa} = rate of formation of PGG_2 (mM/min), in the absence of inhibitor.

K_m of prostaglandin endoperoxide synthase is ≈ 0.6 mM.

V_{max} of prostaglandin endoperoxide synthase is ≈ 51.546mM/min

The Lineweaver-Burk plot/Double reciprocal plot of the competitive inhibition of prostaglandin endoperoxide synthase by Ibuprofen is shown in figure 4, and the straight line equation is given as

$$\frac{1}{V_{oi}} = \frac{\alpha K_M}{V_{max}}\frac{1}{[S]} + \frac{1}{V_{max}} = 0.019970899\frac{1}{[S]} + \frac{1}{51.546}$$

V_{oi} = rate of formation of PGG_2 (mM/min), in the presence of 10mg/ml Ibuprofen inhibitor (Nelson and Cox, 2008b).

$$\alpha = 1 + \frac{[I]}{K_i} \approx 1.71$$

K_i = 14.085, if the unit of inhibitor concentration is mg/ml.

K_{Mapp} (10mg/ml Ibuprofen inhibitor) = αK_M = 1.026 mM.

The equilibria of the enzyme-catalyzed reaction are shown in Figure 5.

CONCLUSION

Food low in cholesterol and saturated fatty acids content but moderate in PUFA should form the chief of the dietary protein sources for people predisposed or vulnerable to atherosclerosis, cardiovascular diseases and obesity. Dietary intake of large amounts of linoleic fatty acids should be avoided by those susceptible to high blood pressure caused by the over-expression of prostaglandin endoperoxidase synthase. Drugs that inhibit prostaglandin endoperoxidase synthase would reduce prostaglandin synthesis in individuals not associated with over-expression of COX, causing hypo-prostaglandinosis which increases the risk of cardiovascular incidences such as heart attack and strokes. Over-expression of COX-2 can be controlled by such drugs as inhibit COX (e.g ibuprofen, vasoprin and aspirin), by which means heart attacks, cardiac arrests, and strokes are prevented in patients suffering from hyper-prostaglandinosis.

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