Review of Literature

1. Prevalence of diabetes mellitus

Diabetes mellitus is growing as an epidemic in both developed and developing countries (Rahman and Rao, 2002). The world wide prevalence data complied by the WHO indicate that the prevalence of diabetes has reached epidemic proportions (King and Rewers, 1998). The global number of people with diabetes mellitus is expected to be at least 220 million in 2010 reaching 324 million by 2025 (Jayakumar and Nisha, 2005).

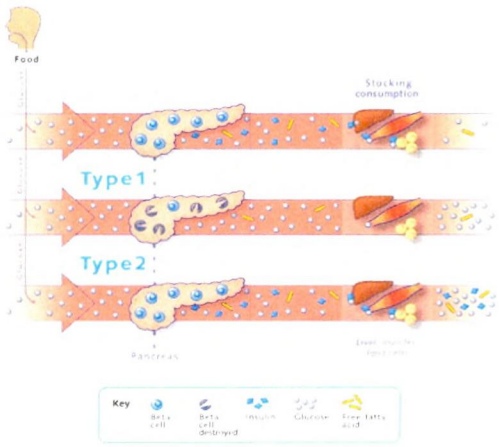
The countries with the largest number of adults with diabetes (in descending order) are India, China, United States, Pakistan, Japan, Indonesia, Mexico, Egypt, Brazil and Italy. The first three countries account for nearly half of the world's population with diabetes and the countries comprising the western Pacific region account for another 44 million people with diabetes (International Diabetes Federation,2001).

According to Green *et al.*, (2005) increase in the number of patients will be most pronounced in nations currently undergoing socio economic development including increasing urbanization. The prevalence of diabetes for all age groups world wide was estimated to be 2.8 per cent in 2000 and 4.4 per cent in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 36 million in 2030 (Wild *et al.*, 2004). More over the prevalence varies within the same population among people of different ethnic descent (Ramankutty *et al*, 2007). The most important demographic change to diabetic prevalence across the world appears to increase in the population of people more than 65 years of age (Wild *et al.*, 2004).

India is the leading country for diabetes, with 31.7 million cases in 2000. It is expected to rise to 79.4 million by 2030. About 90 per cent of cases are Type 2 diabetes (Misra *et al.*,2007 and Neal, 2008). In South India the prevalence of diabetes in adults is 8.21 per cent. Prevalence of Type 2 diabetes is 2.4 per cent in rural population (Ramachandran, 2007) and 25 per cent of these diabetics have a Body Mass Index (BMI) <19 i.e. low body weight (Prabhu *et al.*, 2004).

2. Classification and complications of diabetes mellitus

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997), made recommendations to eliminate the terms Insulin Dependent Diabetes Mellitus (IDDM) and Non Insulin Dependent Diabetes Mellitus (NIDDM) and to keep the terms Type 1 and Type 2 diabetes. Type 1 diabetes mellitus – juvenile diabetes is characterized by beta cell destruction caused by an auto immune process usually leading to absolute insulin deficiency (Hother *et al.*,1997). Type 2 diabetes is a disease of nutrient storage in the context of insulin resistance. The pancreas normally continues to secrete insulin, even at elevated rates, until very late in the disease process. But the insulin resistance related strongly to overweight and physical activity as well as to genetic predisposition which means that blood glucose becomes elevated even in the presence of high circulating insulin (Garrow *et al.*,2000). Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Krause, 2001).



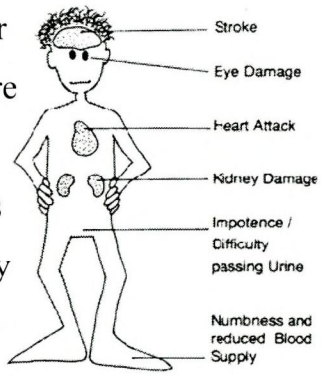
Two types of diabetes

Diabetes mellitus is a condition characterized by high blood sugar level, which in course of time can lead to permanent damage of both large and small blood vessels and the organs supplied by these blood vessels (Neelam and Elizabeth, 2005). Micro and macro vascular complications are responsible for the majority of morbidity and mortality associated with diabetes mellitus (Zanchary and Bloomgarden, 2002).

Type 2 diabetes can cause blindness, kidney disease, heart disease, stroke and nerve damage, which can lead to amputations. It reduces life expectancy by five to seven years, this increases the risk of heart diseases by 50 times, renal

problems by 17 times and gangrene by 25 times (Neelam and Elizabeth, 2005). Type 2 diabetes is an important risk factor for atherosclerotic diseases such as CVD, stroke, Peripheral Vascular Obstructive (PVO) disease, increased non-invasively measured thickness of the intima media layer of common carotid arteries and has been reported in various conditions such as obesity, hypertension and CVD (Oleary and Peter, 2000). Many risk factors associated with diabetes are polycystic ovary syndrome , chronic pancreatitis, hepatic steatosis, cystic fibrosis, neuropathies and myopathies , myotonic dystrophy, ataxia and hypoinsulinism (Raal,2004).

William *et al.*,(2005) opines that people with diabetes are two to six times more likely to have atherosclerosis , putting them at greater risk of heart attack and stroke. Cardiac complications are responsible for 80 per cent of deaths and 75 per cent of hospitalization in diabetic patients. The American Diabetes Association (ADA) reveals that damage to the coronary arteries is two to four times more likely in asymptomatic persons with Type 2 diabetes without apparent heart problems than the same risk for heart diseases with persons without diabetes who had already suffered one heart attack.People with diabetes are four times more likely to become victims of retinopathy (Raal, 2004). According to the ADA after 15 years of diabetes, 97 per cent of Type 1 diabetes and 80 per cent of Type 2 diabetes show evidence of retinopathy.



Complications of diabetes

An estimated 50 per cent of those with diabetes have some form of neuropathy. The highest rates of neuropathy are among people who have the disease for at least 25 years (Ramachandran, 2007).The effect of all these changes in the human body results in an increased blood viscosity, reduced blood flow and decreased delivery of oxygen to tissues ultimately leading to thromobosis (Cushman *et al.*, 1999).Diabetes is the most common cause of kidney failure

accounting for more than 40 per cent of new cases and among the detected primary cases kidney failure accounts for about 43.2 per cent (Robert *et al*, 2004).

Studies conducted by Figarokathleen *et al.,*(2005) revealed that diabetics are exposed to 'Foot diseases" that need serious consideration. About 15 per cent of diabetics have foot ulcer and one out of every eight diabetic patient undergo amputation.

2. Etiology of diabetes mellitus

Many factors like heredity, age, obesity, diet, sex, sedentary lifestyle, socio economic status, hypertension, altered immune function and various stresses are involved in the etiology of diabetes mellitus (Ramachandran *et al.*, 1999 and Khan *et al.*, 2006).

Studies on adults reveal that social and lifestyle factors and environmental factors such as literacy, smoking and stress are the primary causes of diabetes mellitus (Abdul *et al.*,2002). Urbanization may also contribute to insulin resistance (Misia,2004). People who eat fatty foods are less active and are more likely to be the subjects of chronic stress (Adam., 2001).

Ohkuba *et al.*, (2004) opined that the most important morphological factor linked to Type 2 diabetes mellitus is waist – hip ratio, the mark of central adiposity especially in women. Both subcutaneous and visceral adnominal fat areas are independently associated with insulin resistance and visceral fat area are not associated with serum triglycerides (Taniguchi *et al.,*2002).

As Type 2 diabetics show familiar aggregation, twin and family studies have proved the role of the genetic component to be relatively strong (Bennet, 1992). A study carried out by Seshaish *et al.,*(2007) in 356 Type 2 diabetic people showed a positive family history of 32 per cent. Paternal influence is stronger than maternal influence in the transmission of diabetes. Prevalence of diabetes is higher in the offspring of conjugated diabetic patients.

The incidence of diabetes in the offspring of a single diabetic parent is 15 per cent and 60 to 70 per cent when both parents are diabetic (Love Grohe, 1995).

Malnutrition during fetal life could become one of the risk factors for diabetes (Yajnic, 2002).

Patients with hypertension have 28 per cent higher risk of developing diabetes after 3-6 years of therapy (Greess *et al.*, 2000).Individuals who habitually chew beetle, a common practice for more than 2000 million Asians may be at a risk for developing Type 2 diabetes mellitus. Smoking has been found to be an independent risk factor for the development of Type 2 diabetes mellitus (Sahay , 2002). Watching television represents a major sedentary behavior related to risk for diabetes (Health Care Excel., 2000).

Dietary carbohydrate may influence the development of Type 2 diabetes mellitus through effects on blood glucose and insulin concentration (Meyer *et al.*, 2002).

3. Role of diet and nutrients in treating and preventing diabetes mellitus

Nutrition plays a key role in the treatment and prevention of diabetes mellitus, it is effective as well as cost efficient (Toeller, 2005). Montonen *et al.*,(2005) suggested that prevention of Type 2 diabetes might be aided by the consumption of certain foods that are rich in nutrients with hypothesized health benefits (Meltzer *et al.*, 2007).The dietary management should be based on age, sex, weight, height, physical activity, physiological needs and current dietary history of the patients. Diets rich in polyphenols and vitamin A are found to inhibit the development of Type 1 autoimmune diabetes in non obese diabetic mice (Susan and Helseth, 2007).

Dietary management of diabetes should not only aim to achieve glycaemia control, but also to normalize dyslipidemia commonly associated with diabetes. Carbohydrate content of the diet has to provide 50-60 per cent of the calories and most of this is to be in the form of complex carbohydrates with a high fibre content and low glycemic index (Ghafoorunissa and Krishnasamy, 2007). Axelsen *et al.*,(1999) concluded that an increased intake of slowly digestible

carbohydrates exert an overnight second meal effect in patients with Type 2 diabetes.

Protein intake of 0.8g/kg is recommended for diabetics so as to contribute to 12-20 per cent of the total calories. A high protein diet lowers blood glucose postprandially in persons with Type 2 diabetes and improves over all glucose levels. Fasting triacyl glycerol was also significantly lower after the high protein diet (Gannon *et al.*, 2003).

Fat in the diet has to be divided as 50 per cent poly unsaturated and 50 per cent mono unsaturated fats. Healthful diets that avoids excess energy intake and reduces saturated fat consumption are key components of life style management in Type 2 diabetes. The fatty acid profile of healthful Type 2 diabetic diets can be improved by substituting mono unsaturated and poly unsaturated fatty acids for saturates and increasing the consumption of n-3 long chain fatty acids. Increasing the consumption of n-3 PUFA reduces the risk of conversion from impaired glucose tolerance to 'Type 2' diabetes (Franz *et al.*, 2006).

Some studies have found that fish oil supplementation improves glucose tolerance, reduces the high triglyceride and cholesterol levels in people with diabetes (Zak, *et al.*, 1989). Eating fish also may afford some protection from diabetes (Feskens, 1991). Incorporating a fish meal into a weight-loss regimen was more effective than eating fish alone at improving glucose and insulin metabolism and high cholesterol (Morsi, *et al.*, 1999).

Vegetarians have been reported to have a low risk of Type 2 diabetes (Snowdorn, 1985).When people with diabetic nerve damage switched to vegetarian diet improvements have been reported after several days (Crane and Sample, 1998).

A variety of vitamins, minerals, amino acids, antioxidants and other supplements may help with symptoms and deficiencies associated with diabetes. Antioxidants have beneficial role in improving glycemic status of diabetics

suggesting that oxidative stress in diabetes mellitus has a direct relation with blood sugar (Bhasim, *et al.*, 2005).

Alpha lipoic acid is a powerful natural antioxidant. In a preliminary study, supplementation with 600 mg of alpha-lipoic acid per day lowered the progression of kidney damage in patients with Type 2 diabetes (Morcos, *et al.*, 2001).Chromium is also known as diabetic mineral as the main function of chromium in body is to turn carbohydrates into glucose (Anderson *et al.*, 2007). According to Rajpathak *et al.*, (2004) chromium supplements improve glucose tolerance and this brings it to normal. It reduces fasting glucose and insulin levels in gestational diabetes. Anderson *et al,* (2001) stated that chromium supplementation could partially improve the disorders of glucose and lipid metabolism. Vanadium in case of diabetes improves fasting glucose levels. It also increases insulin sensitivity in Type 2 diabetes and lowers the insulin requirement in Type 1 diabetes (Mehmet and Giyasettin, 2006).

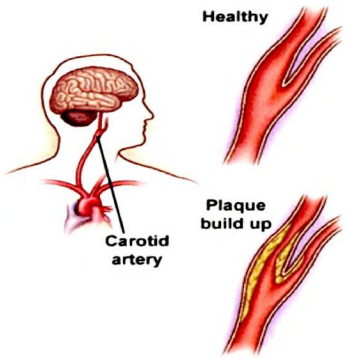
Manganese maintains the blood glucose level in normal ranges and hence useful in treating diabetes and hypoglycemia. Magnesium is mainly important for hypoglycemics because it helps in the digestion of sugar, starches and fats and also helps in stabilizing blood sugar levels (Paolisso *et al.*, 1998). According to Soltani *et al.*, (2005) magnesium could control streptozotocin induced diabetes and prevents its vascular complications. They also stated that chronic magnesium administration may have beneficial effect on diabetes. An inverse relationship between plasma magnesium levels and indices of glycemic control has been noted in Type 1 and 2 diabetes. Zinc is needed for proper release of insulin and hence zinc supplements are beneficial for patients with diabetes (Arthur and Chasemer,1998).

A particular potential benefit of vitamin B supplements for diabetes is mainly its ability to lower blood levels of homocysteine . According to Krone and Ely (2001) diabetic people have low vitamin C level as vitamin C reduces glycosylation. Paolisso *et al.*,(1998) suggest that vitamin C improves glucose

tolerance and significantly reduces urinary protein loss in people with Type 2 diabetes. Vitamin E prevents the destructive vascular damage that occurs in diabetes (Tutunco *et al.*,1999). Vitamin E decreases the requirement of insulin by diabetic people (Manzella *et al.*, 2001). According to Paolisso *et al.*,(1998), vitamin E supplements show improvement in glycemic control and insulin resistance.

B. Hyperlipidemia – the health cracker

Hyperlipoproteinemia or dyslipidemia is the presence of elevated or abnormal levels of lipids and/or lipoproteins in the blood. Lipids are transported in a protein capsule, and the density of the lipids and type of protein determines the fate of the particle and its influence on metabolism. Lipid and lipoprotein abnormalities are extremely common in the general population, and are regarded as a highly modifiable risk factor for cardiovascular disease due to the influence of cholesterol. It is not a disease but a metabolic derangement that can be secondary to many diseases and can contribute to many forms of disease, most notably cardiovascular disease. It is closely related to the terms "hyperlipidemia" and "hyperlipoproteinemia" (National Cholesterol Education Program, 2001). The best known lipoproteins are HDL, LDL, and Very Low Density Lipoprotein (VLDL). Epidemiologic studies have clearly shown that the higher the level of LDL cholesterol, the greater the risk of coronary heart disease. Conversely, the higher the level of HDL cholesterol the lower the risk of coronary heart disease (Mathew, 2000).



Formation of plaque in hyperlipidemia

There are roughly two forms of lipid disorder: Familial Combined Hyperlipidemia (FCH) is the familial occurrence of the disorder, probably caused by polymorphisms in molecules and enzymes that participate in lipoprotein metabolism, such as ApoCII and ApoCIII and Cholesteryl Ester Transferring

Protein (CETP). Combined hyperlipidemia is increasing in frequency and is the most common lipid disorder associated with obesity, insulin resistance and diabetes mellitus. It is associated with other features of the metabolic syndrome including hypertension, hyperuricemia, hyperinsulinemia and highly atherogenic subfractions of lipoprotein remnant particles including small dense low density lipoprotein-cholesterol. Acquired combined hyperlipidemia is extremely common in patients who suffer from other diseases from the metabolic syndrome 'syndrome X', incorporating Type 2 diabetes mellitus, hypertension and central obesity (Grundy *et al.*, 2004).

Abdominal obesity (a waist circumference of more than 40 inches [men] or 35 inches [women]), elevated triglyceride level (150 mg/dL or higher) , low HDL level (less than 40 mg/dl [men] or 50 mg/dl [women]), high blood pressure level (130/85 mm Hg or higher) and high fasting glucose level (110 mg/dl or higher) are the risk factors for the development of hyperlipidemia (Domanski *et al.,* 2004).

Four major classes of medications are used to treat hyperlipidemia. Statin drugs lowers LDL levels by 18 to 55 per cent and triglyceride levels by seven to 30 per cent. They also can raise HDL levels by five to 15 per cent. The bile acid sequestrants lower LDL levels by 15 to 30 per cent, and raise HDL levels by three to five per cent; Nicotinic acid lowers LDL levels by five to 25 per cent and triglyceride levels by 20 to 50 per cent. Nicotinic acid also raises HDL levels by 15 to 35 per cent. Fibric acids lower LDL levels by five to 20 per cent and triglyceride levels by 20 to 50 per cent, and raise HDL levels by 10 to 20 per cent (Sprecher,2006).

1. **Prevalence of hyperlipidemia**

Cardiovascular diseases are the major contributors to global burden of chronic diseases with 29.3 per cent of global deaths and 9.9 per cent of total disease burden. Low and middle-income countries accounted for 78 per cent of the cardiovascular disease deaths. Cardiovascular diseases claim more lives in United States each year than the next four leading causes of death combined, which are

cancer, chronic lower respiratory diseases, accidents and diabetes mellitus (Reddy *et al*.,2006).

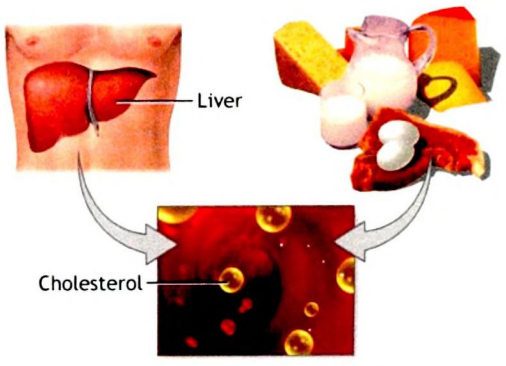
According to the CDPC/National Cholesterol Health Statistics , if all forms of major cardiovascular diseases were eliminated, life expectancy through cardiovascular diseases would rise by almost seven years as the probability at birth of eventually dying from major heart disease is 47 per cent (Steinberger *et al*., 2006).

Chaturvedi *et al* .,(2006) stated that in India , cardiovascular diseases is projected to be the largest cause of death and disability by 2020, with 2.6 million Indians predicted to die due to coronary heart diseases, which constitutes 54.1 per cent of all cardiovascular deaths which are likely to occur among young and middle- aged individuals (30-69 years).

Anand (2000) estimated the prevalence of non-communicable diseases including heart diseases, hypertension, rheumatic fever and stroke as a whole to be 6.6 per cent. Reddy and Yusuf (1998) based on cross sectional survey of urban Delhi, stated that a higher prevalence of coronary heart disease in urban sample was associated with higher levels of Body Mass Index(BMI), blood pressure, fasting blood lipids and diabetes. Incidence and prevalence of coronary heart disease are highest in patients older than 60 years (Lalitha and Prasath, 2005).

2. Etiology of hyperlipidemia

The etiology of cardiovascular disease is multifactorial, such as strong family history, diabetes, obesity, hypertension, hyperlipidemia, lack of exercise, stress and excessive smoking (Jasleen and Kiran ,2005). Carol *et al*., (1999) indicated some environmental factors as causative agents of hyperlipidemia that includes diet high in Saturated Fatty Acids (SFA), excessive calories, alcohol intake, and sedentary life style,



Sources of cholesterol in the body

along with family history, high fat diet, obesity and diabetes. Some other conditions including low thyroid, and drugs, such as B-blockers and cortisone drugs, may lead to hyperlipidemia (Rick and Alan., 2005 and Hennekens *et al.*, 2004). High level of saturated fats in the diet results in an increase in plasma LDL-cholesterol (Tom Brody ,2002).

Hing Man Chan and Grace (2004) found an increase in methyl mercury exposure in population who consumed large amounts of fish. Recent evidence suggests that high mercury content in fish may diminish the cardio protective effect of fish intake. A study conducted by Rabkin *et al.*,(2003) revealed that the prevalence of dyslipidemia is related to BMI, as LDL- cholesterol and triglyceride concentration were higher and HDL- cholesterol concentration lower in those with higher BMI .Women with low levels of HDL- have three times higher risks of dying from cardiovascular diseases.

Affluent living leads to a sedentary life style and this might cause hyperlipidemia (Saucer, 1998). Positive family history is associated with increased incidence of hyperlipidemia and coronary heart disease (Pais *et al.*, 2007 and Deutsch and Morris, 2006).

Zheng *et al.*, (2006) in his research found that a high level of the amino acid, homocystine in the blood increases the risk of cardiovascular diseases very significantly. Primary hyperlipidemia characterised by severe hypertriglyceridemia predisposes to acute pancreatitis (Thompson ,2004).

According to Catelli(2007) the desirable cholesterol level is 150 mg/dl . He states that triglycerides higher than 150 mg/dl are key risk factors for myocardial infarction (Zulet and Martine, 2005).Blood cholesterol concentration is directly related to mortality from coronary heart disease. According to Shiphy *et al.*, (2001) high levels of HDL cholesterol has an inverse relation with myocardial infarction.

Plasma levels of HDL cholesterol are negatively associated with age (Wilson *et al.*, 2004). According to Denke *et al.*, (2004) 25 mg increase in dietary

cholesterol would increase serum cholesterol by one mg/dl. Among the dietary factors non vegetarian food is strongly implicated in the development of dyslipidemia (Williams, 2005).

3. Benefits of diet supplementation in hyperlipidemia

Flax seed rich in linoleic acid and phytoestrogen, lignans and soluble fibres, reduces serum total and LDL cholesterol concentrations, decreases inflammation and rises the omega-3 fatty acids (Bloedon *et al.*, 2004). Flax oil is a rich source of omega-3 fatty acids and about 55 per cent of the oil contains omega -3 fatty acids. It is a good source of fibre which is a phytochemical that helps in treatment of hyperlipidemia (Lalitha and Prasath, 2005).

High intake of vitamin E may slow the development and progression of atherosclerosis (Yusuf *et al.*, 2000). Vitamin E occurring in LDL particles in the blood stream along with other antioxidants, normally acts to reduce or minimize the trend to atherosclerosis (Ganton, 1999).Dietary intake of different antioxidants and high concentration in serum lowers the risk of coronary heart disease by 20 to 40 per cent (Julie *et al.*, 1997).

Kris *et al.*,(2001) have shown the beneficial effects of nut consumption. Total cholesterol and LDL cholesterol get reduced because nuts are rich in unsaturated fatty acids and low in saturated fatty acids. Studies performed by Sacks *et al.*, (1998) show that total cholesterol, LDL, VLDL and triglyceride levels are higher in non-vegetarians than vegetarians.

Epidemiologic studies have shown a beneficial association between PUFA, principally linoleic acid (c18:2, n-6) intake and cardiovascular disease mortality and morbidity. PUFA, is most potent and has cholesterol lowering capacity with favourable effect on postprandial lipemia. LDL cholesterol is reduced when saturated fats are replaced with PUFA or with carbohydrates. The percentage of energy derived from fat is recommended to be 30 per cent (Penny *et al.*, 2004).

Linoleic acid found in a variety of vegetable oils, including corn, sunflower and safflower reduces the risk of cardiovascular diseases (David *et al.*,1999). The

effects of higher intake of Mono Unsaturated Fatty Acids (MUFA) from olive oil include a wide range of healthy benefits (Sridevi , 2006).The MUFA, oleic acid (found in olive oil) reduces cholesterol levels and presumably coronary heart disease risk (Nelson ,1998)

Fish oils are especially rich in the omega-3-fatty acids, ecoso pentaonic acid and decoso hexanoic acid (Soyland , 1999). Moderate consumption of fish (1-2 meals /week) lowers the risk of cardiac death in humans (Nancy ,1998).Fish oil supplementation has anti – atherogenic factor. The benefits include increased HDL cholesterol concentrations, reduced triacylglycerol- rich lipoprotein concentrations, reduced postprandial lipemia and reduced remnant concentrations (Paul, 2000).

Recent findings indicate that cocoa and chocolate when processed appropriately, may contain large amounts of flavanoids, particularly, catechin and epicatechin (Merlin and Dennis, 2005). Sara and Kim (2006) concluded that consumption of chocolate and almonds improved serum triacylglycerol levels.

Krest and Yanwen (2003) stated that policosanols are mixture of aliphatic alcohols derived from purified sugarcane. When administered 5-20 mg/day decreases risk of atheroma formation by reducing platelet aggregation, and it also lowers total cholesterol and LDL levels. Recent study has shown that phenolic compounds in red wine inhibit susceptibility of LDL to oxidation thereby reduces the atherogenicity (Renaud *et al.*, 1993).

Isabelle *et al.*, (2003) indicated that soy isoflavones possess hypocholesterolemic effect. Soya rich in isoflavones reduces plasma cholesterol and LDL levels. Soy protein and isoflavones may improve endothelial function and attenuate events leading to lesion and thrombus formation (Susan *et al.*, 1998).

Consumption of 750 ml orange juice daily increased HDL-cholesterol concentrations by 21 per cent, triacylglycerol concentrations by 30 per cent and folate concentrations by 18 per cent decreased LDL:HDL cholesterol by 16 per cent (Elzbieta ,2000).

Charles Melissa (2000) indicated in a recent study that feeding a diet high in carbohydrate delays VLDL clearance. Same diet fed to mildly hyperinsulinemic subjects delays both VLDL and chylomicron clearance without effecting triglyceride production. Supplementation of 20mg of psyllium husk twice a day was found to be most effective in significantly lowering blood lipid profile of hypercholesterolemic patients (Shailaja and Chane, 2005).

Joanne (2006) depicted the implications relevant to fig consumption as figs are richest source of dietary fibre (12.4 %). Dietary fibre has also been shown to be effective in reducing serum cholesterol and it may decrease the risk of CVD by decreasing serum lipids. Plant sterols and stanols have a great potential in cardiovascular risk management. Kay *et al* .,(2004) found out that the total cholesterol was significantly lower when the diet contained three or six grams beta- glucan per day from barley, with the greatest change occurring in men and post menopausal women. Large LDL and small VLDL fractions significantly decreased when whole grains were incorporated into the diets.

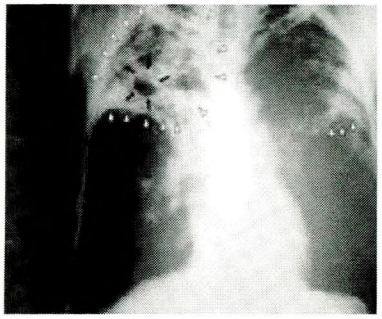
Several of the nutrients in cereals such as linoleic acid, fibre, vitamin E, selenium and folate have known potential for reducing risk factors for CVD. Cereals also contain phytoestrogens of the lignan family and several phenolic acids with antioxidant properties. Processing generally reduces the content of these nutrients and bio-protective substances. Further a study on 337 subjects concluded that a reduction in heart attack risk was attributable to a higher intake of cereal fibre (Truswell,2002).

Regular physical activity of 45-60 minutes per day prevents unhealthy weight gain and obesity. Regular physical activity, healthy diet and avoiding unhealthy weight gain are effective and safe ways to prevent and treat cardiovascular diseases and reduce premature mortality Morris *et al.*,(2003).

C. Tuberculosis- the human waster

Tuberculosis (TB) is a common and deadly infectious disease caused by mycobacteria, mainly *Mycobacterium tuberculosis*. Tuberculosis most

commonly attacks the lungs (as pulmonary TB) but can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, bones, joints and even the skin. Other mycobacteria such as *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium canetti*, and *Mycobacterium microti* can also cause TB, but these species do not usually infect healthy adults (Raviglione and O'Brien ,2004). One-third of the world's current population has been infected by TB, and new infections occur at a rate of one per second (WHO,2008). Not everyone infected develops the full-blown disease; asymptomatic, latent infection is most common. However, one in ten latent infections will progress into active disease, which, if left untreated, kills more than half of its victims.

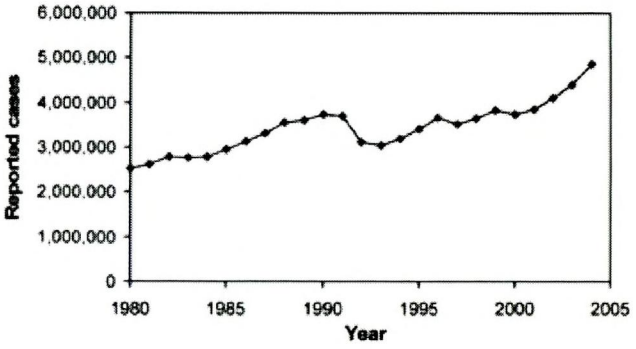


X-ray view of pulmonary tuberculosis

The primary cause of TB, *Mycobacterium tuberculosis* (MTB) is an aerobic bacterium that divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour(Cox,2004). Since MTB has a cell wall but lacks a phospholipid outer membrane, it is classified as a gram-positive bacterium. However, if a gram stain is performed, MTB either stains very weakly gram-positive or does not retain dye due to the high lipid and mycolic acid content of its cell wall (Madison,2001). MTB is a small rod-like bacillus that can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured *in vitro* (Parish and Stoker,2001).

Other known pathogenic mycobacteria include *M. leprae*, *M. avium* and *M. kansasii*. The last two are part of the Non Tuberculous Mycobacteria (NTM) group. NTM cause neither TB nor leprosy, but they do cause pulmonary diseases resembling TB (Neimann *et al.,* 2007).

1. Prevalence of tuberculosis



Global incidence of tuberculosis

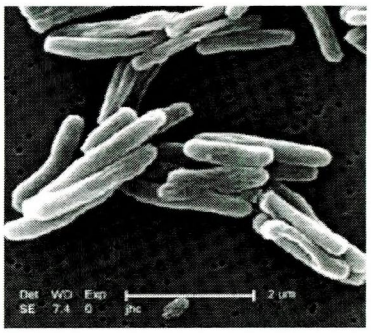
According to WHO one third of the world's population have been exposed to the tuberculosis pathogen. Annually, eight million people become ill with tuberculosis, and two million people di(2006). In 2004, around 14.6 million people had active TB disease with nine million new cases. The annual incidence rate varies from 356 per 100,000 in Africa to 41 per 100,000 in America (WHO,2006). Tuberculosis is the world's greatest infectious killer of women of reproductive age and the leading cause of death among people with Human Immunodeficiency Virus (HIV) (Piramanayagam, 2007).

India has the largest number of infections, with over 1.8 million cases. The incidence of TB varies with age. In Africa, TB primarily affects adolescents and young adults. However, in countries where TB has gone from high to low incidence, such as the United States, TB is mainly a disease of older people (WHO,2006).There are a number of known factors that make people more susceptible to TB infection: worldwide the most important of these is HIV. Co-infection with HIV is a particular problem in Sub-Saharan Africa, due to the high incidence of HIV in these countries (Chaisson and Martinson, 2008). Smoking more than 20 cigarettes a day also increases the risk of TB by two to four times (Davies *et al.*, 2006 and Jha *et al.*, 2008). Diabetes mellitus is also an important risk factor for TB that is growing in importance in developing countries (Restrepo,2007) .

Nearly 400,000 deaths in India are caused by TB each year, and it is the leading cause of death in the 15 to 45 age group. The increasing prevalence of HIV infection, which makes people more susceptible to TB and drug resistant types of TB, means the disease will pose an increasingly serious health hazard

with high economic burden for India. The estimated direct and indirect cost of tuberculosis to the country is $3 billion per year. Around 325,172 people in India had died of the disease in 2005 alone (WHO,2007).Of all fresh cases in the country, 1.2 per cent were infected with HIV and 2.8 per cent of all new cases have been diagnosed with multi-drug resistant TB (MDR-TB) and 30 per cent of the cases were not even detected in the country (WHO ,2006).

2. Transmission and progression of tuberculosis



Mycobacterium tuberculosis

When people suffering from active pulmonary TB cough, sneeze, speak, kiss, or spit, they expel infectious aerosol droplets 0.5 to 5 µm in diameter (CDPC, 2008). A single sneeze, for instance, can release upto 40,000 droplets (Cole and Cook, 2006). Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and the inhalation of just a single bacterium can cause a new infection (Nicas *et al.*,2005). People with prolonged, frequent, or intense contact are at particularly high risk of becoming infected, with an estimated 22 per cent infection rate. A person with active but untreated tuberculosis can infect 10–15 other people per year (WHO,2006). Others at risk include people in areas where TB is common, people who inject drugs using unsanitary needles, residents and employees of high-risk congregate settings, medically under-served and low-income populations, high-risk racial or ethnic minority populations, children exposed to adults in high-risk categories, patients immunocompromised by conditions such as HIV/AIDS, people who take immunosuppressant drugs, and health care workers serving these high-risk clients (Griffith and Kerr, 2006).

The chain of transmission can be broken by isolating patients with active disease and starting effective anti-tuberculous therapy. After two weeks of such treatment, people with non-resistant active TB generally cease to be contagious (Kaufmann ,2002).

Progression from TB infection to TB disease occurs when the TB bacilli overcome the immune system defenses and begin to multiply. However, in the majority of cases, a latent infection occurs that has no obvious symptoms. These dormant bacilli can produce tuberculosis in two to twenty three per cent of these latent cases, often many years after infection. In patients co-infected with *M. tuberculosis* and HIV, the risk of reactivation increases to 10 per cent per year (Parrish *et al.,* 1998).

Other conditions that increase risk include drug injection, mainly due to the lifestyle of intravenous drug users; recent TB infection or a history of inadequately treated TB; chest X-ray suggestive of previous TB, showing fibrotic lesions and nodules; diabetes mellitus; silicosis; prolonged corticosteroid therapy and other immunosuppressive therapy; head and neck cancers; hematologic and reticuloendothelial diseases, such as leukemia and hodgkin's disease; end-stage kidney disease; intestinal bypass or gastrectomy; chronic malabsorption syndromes or low body weight (CDPC,2003).

3. Role of nutrition in tuberculosis

Diet therapy is concerned with the modification of the normal diet to meet the requirements of the sick individual. Dietary adjustments in TB patients help manage symptoms of the infection better (Ferguson *et al.*, 2000).

With profound weight loss, cachexia, nutrient deficiencies and malnutrition complicating the course of tuberculosis, medical nutrition therapy is a critical aspect of treatment (Niyongabo, 2002).

Most of the host defense mechanisms are altered in protein calorie malnutrition, as well as during deficiencies of trace elements and vitamins as seen in tuberculosis (Ben and Goldin,2002).Patients with PCM show impaired lymphocyte proliferation, reduced antibody affinity and phagocyte dysfunction coupled with profound wasting. Supplementation of several amino acids like leucine, I- glutamine and l-arginine for eight weeks, resulted in significant weight gain in patients with tuberculosis (Zachary and Bloomgarden *et al.*,2002).

In a randomized trial, daily supplementation with 180mg of a carotene for four weeks in TB individuals was associated with small increase in total WBC count and increase in CD_4 cell count (Porter *et al.*,2008). In a placebo trial in South Africa among children infected with TB , vitamin A supplementation resulted in approximately 50 per cent reduction in diarrheal morbidity (Paton *et al.*,2002).

Several research studies have indicated that the apoptosis of CD_4 cells does not result solely from TB infection, but largely from antioxidant imbalances of free radicals and oxidizing agents in the host (Larouze *et al.,* 1999). These reactive oxygen species can be reduced by restoring proper redox balance through adequate availability of antioxidants (Lettow *et al.*,2007). Nutrients like beta – carotene , ascorbic acid , tocopherols , selenium and zinc are dietary antioxidants used as supplements for the prevention and treatment of TB (Karyadi *et al.*,2000). Several B complex vitamins have roles in immune functions. Vitamin B_6 deficiency results in failure of several components of both cell mediated and humoral immune response (Achim *et al.*,2004). Riboflavin deficiency has been shown to impair the ability to generate antibodies. Clinical studies have shown that individuals with low serum vitamin B_{12} had impaired neutrophil function (Ilich *et al.*,2003).

Vitamin C deficiency impairs phagocytosis and cell mediated immune reactions in the infected. Vitamin C as a free radical scavenger , works synergistically with vitamin E, regenerating it as it becomes depleted. Proliferation of T and B lymphocytes with decreased rates of infections were seen following its supplementation in a study (Semba *et al.*,1992).

Vitamin E as a master antioxidant that assists the helper T cells withstand the attack and fight the TB virus. It makes replication of TB virus more difficult by reducing production of inflammatory compounds. In an European study vitamin E reversed to a large extent the toxic bone marrow cells of patients with progressive TB infection (Hernandez,2008)

Zinc, the deficiency of which generates lymphoid atrophy and reduces lymphocyte responses, when supplemented, had resulted in significant reduction in the severity of diarrhea in the infected (Zachariah and Bloomgarden,2002). Deficiency of vitamin E is associated with impaired phagocytosis, decreased CD_4 cells and occurrence of opportunistic infections (Van *et al.*,2000). Increased intake of iron , vitamin E and riboflavin significantly reduced the hazards of TB , while in a study in San Francisco, higher dietary intake of zinc , thiamine , niacin and riboflavin were positively related to CD_4 cell counts (Seyedrezazadeh *et al.*,2008).It seems therefore that nutrition is an important factor in the prevention of tuberculosis. It is also likely that diet contains a specific nutritional factor which enhances natural resistance under certain conditions.

D. Significance of wheat germ, bran and grass

In many studies, eating whole grains, such as whole wheat, has been linked to protection against atherosclerosis, ischemic stroke, diabetes, insulin resistance, obesity, and premature death. Whole grains are excellent sources of fibre. In the meta-analysis of seven studies including more than 150,000 persons, those whose diets provided the highest dietary fibre had a 29 per cent lower risk of cardiovascular disease compared to those with the lowest fibre intake (Lopez *et al.*, 2003).

In addition to the matrix of nutrients in their dietary fibres, the whole-grain arsenal includes a wide variety of additional nutrients and phytonutrients that reduce the risk of cardiovascular disease. Compounds in whole grains that have cholesterol-lowering effects include polyunsaturated fatty acids, oligosaccharides, plant sterols and stanols, and saponins (Bach *et al.*,2003).

The FDA permits foods that contain at least 51 per cent whole grains by weight to display a health claim stating consumption is linked to lower risk of heart disease and certain cancers. Now, research suggests regular consumption of whole grains also reduces risk of Type 2 diabetes . Risk of Type 2 diabetes was 31 per cent lower in black women who frequently ate whole grains, a rich source of

magnesium compared to those eating the least of these magnesium-rich foods (Van *et al.*,2007).

Whole grains are also important dietary sources of water-soluble, fat-soluble, and insoluble antioxidants including vitamin E, tocotrieonols, selenium, phenolic acids, and phytic acid. The high antioxidant capacity of wheat bran is 20 folds that of refined wheat flour. Antioxidants are associated with significant protection against cardiovascular disease (Mc Keown *et al.*,2005).

Like soybeans, whole grains are good sources of phytoestrogens, plant compounds that may affect blood cholesterol levels, blood vessel elasticity and bone metabolism. Whole grains are rich sources of lignans that are converted by the human gut to enterolactone and enterodiole. Blood levels of enterolactone have been found to have an inverse relation not just to cardiovascular-related death, but to all causes of death, which suggests that the plant lignans in whole grains may play an important role in their protective effects. Lower insulin levels may also contribute to the protective effects of whole grains. In many persons, the risks of atherosclerotic cardiovascular disease, diabetes, and obesity are linked to insulin resistance (Erkkila *et al.*,2005).

Wheat, in its natural unrefined state, features a host of important nutrients. Therefore, to receive benefit from the wholesomeness of wheat it is important to choose wheat products made from whole wheat flour. The health benefits of wheat depend entirely on the form in which it is consumed. In the process of making 60 per cent extraction flour, over half of the vitamin B_1, B_2, B_3, E, folic acid, calcium, phosphorus, zinc, copper, iron, and fibre are lost (Anderson *et al.*,2007). An account of the health benefits of wheat bran, wheat germ and wheat grass is given below:

1. Wheat germ

Wheat kernel contains two to four per cent germ, also called embryo, which is separated from the

Wheat germ

endosperm by milling operations like rolling , sieving etc. In the wheat germ most nutrients with the exception of starch are concentrated. Other remarkable non nutrients

of wheat germ are the methyoxy- substituted lemoquinones which are present as glycosides of the corresponding methyoxyhydroquinones. These compounds have been reported to exert anti cancer effects in experimental systems (Farkas *et al.*,2002).

Illmer *et al.*,(2005) revealed that each tiny kernel is packed with important minerals such as zinc and potassium as well as several B vitamins. Wheat germ also has high oil content and subsequently a high amount of vitamin E a powerful antioxidant. Vitamin E not only protects fats, cholesterol and cell membrane from damage, but also helps in immune system functions, cancer prevention and blood glucose control.

Azzuzabala (1997) proved that wheat germ improves heart health. Wheat germ oil contains linoleic (approximately 40 % of saturated fatty acid content) and linolenic acids (5 %), the precursors for the omega 6 and omega 3 essential fatty acids , respectively. Beneficial effects from wheat germ oil may also be due to a combination of its vitamin E , octacosonol and essential fatty acid contents.

The *in vitro* and *in vivo* effects of a fermented wheat germ extract has been demonstrated to induce apoptosis in pancreatic carcinoma cells, T and B lymphocytic tumor cell lines and leukaemia cells in mice. In lymphoid tumor cells, apoptosis was selectively induced via thyrosine phosphorylation and calcium ion influx (Wettstein, 1995).

Nakatsuma (2001) opined that the oral administration of wheat gem extract with conventional treatments helped to improve the clinical outcome of colon cancer treatment when compared with treatment with conventional regiemers alone and at the same time demonstrated no signs of toxicity. Fleming *et al.,* (2001) reported that the fat soluble compounds naturally occurring in wheat germ suppress oxidative DNA damage that can contribute to abnormal

uterine growth. Gratacas (1999) studied the liphophilic factor (vitamin E) found in wheat germ by exploring the relationship of plasma vitamin E and circulating and placental levels of lipid peroxides to chronic hypertension and preeclampsia during pregnancy among healthy pregnant women, with uncomplicated chronic hypertension and pregnant women with chronic hypertension.

Kharb (2000) found that vitamin E in wheat germ extract significantly reduced endothelial cell activation and placental insufficiency in preeclamptic women. Vitamin E from natural sources appears to be particularly bio available , as the placenta delivers it much more efficiently to the fetus than that it does through synthetic form. Cara *et al.*,(1992) investigated the possible effects of wheat germ supplementation on lipid metabolism in humans. After four weeks of supplementation, glycemia did not change but the total plasma cholesterol, Apolipoprotein B and A_1 significantly decreased. In the hypertriglyceridemia subjects, it was accompanied by a significant reduction of plasma triglycerides and the study pointed out that wheat germ may play a beneficial role in the dietary management of hyperlipidemia. Clinical studies using fermented wheat germ extract as a supplement to drug therapy in cancer patients at doses of 8.5g/day showed a reduction in the side effects of chemotherapy and concluded that it causes no adverse effects under the conditions of its intended use as an ingredient dietary supplements (Heimbach *et al* .,2007).

2. Wheat bran

Higher intake of wheat bran is associated with increased sensitivity to insulin in population studies and clinical trials, because wheat bran improves insulin sensitivity by lowering the glycemic index of the diet while increasing its content of fibre, magnesium and vitamin E (Chandalia ,2000).

Wheat bran

Studies suggest that a diet added with wheat bran may help prevent Type 2 diabetes, lower insulin and blood sugar levels, and improve cholesterol and triglyceride levels in people with diabetes. In addition, one well-designed study

suggests that pregnant women with 'Type 1'diabetes are able to lower the amount of insulin they use if they include wheat bran in the diet (Gallaher and Schneeman ,1996).

Researchers in the UK Women's Cohort Study found a diet rich in fibre from wheat bran offered significant protection against breast cancer for pre-menopausal women (Cade *et al.*,2006). Pre-menopausal women eating wheat bran (>30 g daily) halved their risk of developing breast cancer compared to women whose diets supplied the least fibre (<20 g/day).

The fibre content of wheat bran, fills the stomach and leaves little room for foods containing fat. These fibres have been shown to actually absorb cancer-causing substances and leave the body in the stool. While all women (and men too) need the hormone estrogen, too much can lead to cancer, especially of the uterus and breast. Eating a diet high in wheat bran can bind or soak up the excess estrogen, increasing the rate at which it is excreted from the body (Rose *et al.*, 1997). Borel *et al.*, (2000) investigated the effects of fibre-rich wheat bran on dietary fat and cholesterol assimilation. Plasma lipids and cholesterol significantly decreased by wheat bran which alters fat and cholesterol processing in rats.

Wheat bran supplies enough linoleic acid, which is a primary member of omega-3-fatty acid (Franz *et al.*,1998).Wheat bran and cellulose pores have significant influence on serum cholesterol. Hypercholesterolemia effects of these fibres include altered intestinal absorption, metabolism and release of cholesterol (Corinne *et al.*, 1997).

The serum triglyceride response was lower in the presence of wheat bran. Chylomicron and triglycerides were reduced with wheat fibre intake. Cholesterolemia decreased postprandially for six hours and was further lowered in the presence of wheat bran (Cara *et al.*, 1992).

Gayla and John (1995) indicated that wheat bran and brewers yeast taken daily may be helpful in preventing heart trouble. Smolin (1999) stated that safest

supplements for lowering cholesterol probably are soluble fibres such as wheat bran.

3. Wheat grass

Wheat grass is a humble grass obtained from red wheat which is full of nutrients and vitamins for the human body. In the form of fresh juice it has high concentrations of chlorophyll , active enzymes, vitamins and other nutrients, hence referred as the " the green gold" (Fahey *et al.*,2005).Jensen *et al.*,(2005) opines that the three most important effects of wheat grass on the human body are blood purification, detoxification and colon cleaning. This is because wheat grass is the richest source of vitamins A,B,C,E and K. Wheat grass juice has over 90 minerals which are needed to maintain good metabolism. The presence of minerals found in wheat grass such as calcium, magnesium , potassium and iron makes it very effective. Organic sodium is also found aiding in digestion and regulating the amount of fluids in the body. The protein contained in young grass is more easily assimilated because of its small size and completeness in nature. Fresh wheat grass juice contains enzymes such as protease, cytochrome, oxidase, amylase, lipase, transhydrogenase and superoxide dismutase (Davis *et al.*,1999).

Wheat grass

Chlorophyll is concentrated sun power and the chlorophyll molecule found in wheat grass closely resembles that of the haem (Ferruzzia and Blakesleeb,2007). "The American Journal of Surgery", recommends chlorophyll for its antiseptic benefits. The study suggests the following clinical uses for chlorophyll, such as healing wounds, curing chronic sinusitis, helps purify the liver, neutralize strep infections, reduce fevers, cure advance pyorrhea in many cases and improves the blood sugar problems (Benjamin, 2006).

Ben and Goldin (2002) reveal that daily use of chlorophyll is most beneficial, at least to a certain degree, and in combination with other accepted

methods of treatment in hardening of the arteries, high blood pressure and even in arthritis. It seems that the ability of chlorophyll to combine with oxygen and its cleansing ability contributes much to the removal of foreign matter from the walls of the blood vessels thus bringing the desired relief. Wheat grass contains 70 per cent crude chlorophyll which can protect against carcinogens (De Vogel *et al.* ,2005).

Phytochemicals are the subject of intense scientific research focusing on the prevention and treatment of chronic diseases especially diabetes mellitus. Phytochemicals are biologically active, naturally occurring chemical components in plant foods such as carotenoids, chlorophyll etc (Melina and Davis,2003). The carotenoids a class of phytochemicals present in wheat grass juice may help to reduce high blood sugar level. Wheat grass has demonstrated antibiotic antioxidant and anti- inflammatory effects (Meyerowitz *et al.*,2003).Wheat grass juice is a safe effective and extremely potent aid to weigh loss. It works by suppressing appetite and stimulating metabolism and circulation (Sunil *et al.* ,2006).

Gurndy *et al.*,(2004) stated that there is an inverse relationship between beta carotene and Type 2 diabetes mellitus. Beta carotene present in wheat grass may reduce symptoms of diabetes and reduce the risk of associated complications. The high therapeutic measure of vitamin E contained in wheat grass reduces high blood sugar level, strengthen the heart and blood vessels and improves the sexual performance (Soumitra *et al.,*1999).

According to People *et al.*,(2000) an inverse association exists between plasma vitamin C levels and increased blood sugar level. The high vitamin C oxidative stress was alleviated by adding vitamin C which rises the levels of nitric oxide.Vitamin C present in wheat grass was more effective in improving blood glucose and insulin metabolism (Saunders ,2002). Vitamin C helps in the conversion of cholesterol to bile acids which can indirectly induce diabetes mellitus (Nagai *et al*,1983).Traceable amount of vitamin E and C present in wheat

grass juice included in the diet ensures better glycemic control (Ziegler *et al.*, 1999).

Folic acid reduces the blood level of homocysteine known as a risk factor of diabetic heart disease and hyperlipidemia. Wheat grass juice contains significant concentrations of folic acid, which may lead to improved insulin production. Magnesium deficiency may increase the risk of Type 2 diabetes mellitus and the magnesium present in wheat grass juice protects against the increased blood glucose levels. Magnesium deficiency leads to free radical accumulation resulting in oxidative injury (Kharab,2001) .

Wheat grass is a complete food in itself and anybody can subsist on it alone for the whole of his life .Wheat grass juice benefits the blood cells, bones, glands, kidney , liver, spleen, muscle, teeth, hair and other parts . It also protects the lungs and blood from air and water pollution, cigarette smoke, toxins and heavy metals. The juice has been reported to cure many ailments such as hypertension , obesity , stomach ulcer, gastritis, liver diseases, asthma, constipation, haemorrhoids, anaemia and hyperlipidemia . The wheat grass juice is helpful for any ailment from cancer to the common cold. It is helpful after surgery or delivery, when the body needs to regain blood levels and build up tissues (Gala *et al.*,1999).