CHAPTER 2

REVIEW OF RELATED LITERATURE

In order to have a better insight into the field in which the investigator is working, an attempt is made to review some prevailing literature in the area pertaining to the study, “Effect of Soya and Caralluma on obese postmenopausal subjects”. It consists of the following aspects.

2.1 Obesity- a global pandemic

2.2 Definition of obesity

2.3 Prevalence of obesity

2.4 Diagnosis of obesity

2.5 Mechanisms involved in body weight regulation.

2.6 Etiology of obesity

2.7 Complications of obesity

2.8 Obesity in relation to cardiovascular disease (CVD) and lipoprotein profile.

2.9 Obesity, hypertension and Coronary Heart Disease (CHD)

2.10 Obesity, Coronary Heart Disease (CHD) and menopause

2.11 Management of obesity

2.12 Soya, a source of dietary protein and obesity

2.13 Caralluma and obesity
### 2.1 OBESITY- A GLOBAL PANDEMIC

“Obesity itself has become a lifelong disease,  
Not a cosmetic issue nor a moral judgement, 
And it is becoming a dangerous epidemic.”

(Eckel et al, 1998).

Obesity is no longer regarded as an aesthetic issue (or) merely a health problem. It is now medically viewed as a full-fledged disease that is reaching epidemic proportions across the developed world. It has been directly linked with many chronic ailments (NIH, 1998).

Since women are at risk of gaining weight as they age, the post-menopausal women become the vulnerable population. Also, they are more at risk for being overweight (or) obese than men. The relative risk for mortality among overweight and obese women (BMI $\geq 27$) was one and one-half to two times that of leanest women (BMI $<19$) (Manson et al, 1995). A national survey had shown that a fifth of adults are overweight and 6% are obese (Mudur, 2003).

Hormonal changes of menopause result in central (or) abdominal fat. Menopause is associated with modest increase in total fatness and accelerated accumulation of abdominal body fat. Abdominal fat gain is associated with increases in cholesterol levels, BP, CVD, type 2 diabetes, breast cancer and arthritis. Excess abdominal and upper body adiposity is associated with a particularly high risk of CHD in women (Bjorntorp, 1985).

Obesity is a burgeoning public health problem that will strain across health care services and increase the incidence of heart disease and diabetes across South Asia. The risk of obesity is highest among 20% of population in India that consumes 80% of visible dietary fat. High fat intake and sedentary life styles are the factors fuelling an urban and rural person which causes a rise in obesity (Mudur, 2003).

Obesity identified as a nutritional disorder, thirty years ago, still continues to be one of the most important, yet preventable health hazards (WHO, 2003). Healthy people 2010 objective is to increase the proportion of adults who are at healthy
weight and to reduce the proportion of adults who are obese (Mahan, 2004). Obesity should therefore be of significant public health concern throughout the developing and developed world (Nisha, 2006).

2.2 DEFINITION OF OBESITY

Obesity may be defined as a state of imbalance between calories ingested versus calories expended which would lead to excessive (or) abnormal fat accumulation (Nammi et al, 2004). Obesity is also defined as a condition of excessive fatness, either generalized (or) localized (Mahan, 2004).

2.3 PREVALENCE OF OBESITY

Obesity rates have now reached epidemic proportions with over 25% of the population being obese in US and 15% in Europe (Chopra et al, 2002). According to NHANES survey 1999-2000 an estimated 64% of people in US are overweight (or) obese, with 34% in overweight category and an additional 27% in the obese category (Schills, 2006).

Obesity affects male and female, all races and ethnicities and all age groups. The prevalence in non-hispanic white women was 23% and women of lower socio-economic status (50%), high school education (25.3%) compared to college education (14.3%) is more (Schills, 2006).

More women than men are in the obese category. In NHANES 1999-2000, obesity rates were higher in African-American women (49.7%) than men (28.1%). Similarly higher obesity rates were observed in Hispanic women (39.7%) than in men (28.9%). The age adjusted prevalence of obesity was 30.5% in 1999-2000 compared with 22.9% in NHANES III (1988-1994; P<.001) (Flegal, 2002). Around eight million people (22%) in UK were obese in 2008. Recent studies suggest that nearly 15-20% of the middle aged European population are obese (Nammi et al, 2004).

In the developing countries, in the relatively affluent and urbanized societies, there is a rapidly increasing prevalence of obesity (Desai, 2000). India is following a trend of other developing countries that are steadily becoming more obese. Morbid obesity has acquired epidemic proportions in the country with 5% of the population suffering from it (Desai, 2000).
Table 2.3
States of India ranked in order of percentage of people who are overweight (or) obese.

<table>
<thead>
<tr>
<th>State</th>
<th>Males (%)</th>
<th>Males rank</th>
<th>Females %</th>
<th>Females rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Punjab</td>
<td>30.3</td>
<td>1</td>
<td>37.5</td>
<td>1</td>
</tr>
<tr>
<td>Kerala</td>
<td>24.3</td>
<td>2</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Goa</td>
<td>20.8</td>
<td>3</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>19.8</td>
<td>4</td>
<td>24.4</td>
<td>4</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>17.6</td>
<td>5</td>
<td>22.7</td>
<td>10</td>
</tr>
<tr>
<td>Sikkim</td>
<td>17.3</td>
<td>6</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Mizoram</td>
<td>16.9</td>
<td>7</td>
<td>20.3</td>
<td>17</td>
</tr>
<tr>
<td>Himachal Pradesh</td>
<td>16</td>
<td>8</td>
<td>19.5</td>
<td>12</td>
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<tr>
<td>Maharashtra</td>
<td>15.9</td>
<td>9</td>
<td>18.1</td>
<td>13</td>
</tr>
<tr>
<td>Gujarat</td>
<td>15.4</td>
<td>10</td>
<td>17.7</td>
<td>7</td>
</tr>
<tr>
<td>Haryana</td>
<td>14.4</td>
<td>11</td>
<td>17.6</td>
<td>6</td>
</tr>
<tr>
<td>Karnataka</td>
<td>14</td>
<td>12</td>
<td>17.3</td>
<td>9</td>
</tr>
<tr>
<td>Manipur</td>
<td>13.4</td>
<td>13</td>
<td>17.1</td>
<td>11</td>
</tr>
<tr>
<td>Ind Ore</td>
<td>12.1</td>
<td>14</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Uttarkhand</td>
<td>11.4</td>
<td>15</td>
<td>14.8</td>
<td>14</td>
</tr>
<tr>
<td>Arunachal Pradesh</td>
<td>10.6</td>
<td>16</td>
<td>12.5</td>
<td>19</td>
</tr>
<tr>
<td>Uttat Pradesh</td>
<td>9.9</td>
<td>17</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Jammu &amp; Kashmir</td>
<td>8.7</td>
<td>18</td>
<td>11.1</td>
<td>5</td>
</tr>
<tr>
<td>Bihar</td>
<td>8.5</td>
<td>19</td>
<td>10.5</td>
<td>29</td>
</tr>
<tr>
<td>Nagaland</td>
<td>8.4</td>
<td>20</td>
<td>10.2</td>
<td>22</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>8.4</td>
<td>20</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Meghalaya</td>
<td>8.2</td>
<td>22</td>
<td>8.9</td>
<td>26</td>
</tr>
<tr>
<td>Orissa</td>
<td>6.9</td>
<td>23</td>
<td>8.6</td>
<td>25</td>
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<tr>
<td>Assam</td>
<td>6.7</td>
<td>24</td>
<td>7.8</td>
<td>21</td>
</tr>
<tr>
<td>Chattisgarh</td>
<td>6.5</td>
<td>25</td>
<td>7.6</td>
<td>27</td>
</tr>
<tr>
<td>West Bengal</td>
<td>6.1</td>
<td>26</td>
<td>7.1</td>
<td>16</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>5.4</td>
<td>27</td>
<td>6.7</td>
<td>23</td>
</tr>
<tr>
<td>Jharkhand</td>
<td>5.3</td>
<td>28</td>
<td>5.9</td>
<td>28</td>
</tr>
<tr>
<td>Tripura</td>
<td>5.2</td>
<td>29</td>
<td>5.3</td>
<td>24</td>
</tr>
</tbody>
</table>

(Yajnik, 2007)

Mohan et al, 2006 in a Chennai based urban population study found that the prevalence of obesity was 22.8-31.8 % and that of abdominal adiposity was 21.5-36.5%.

Several research works done in India, focus on the fact that obesity among women is common even in the low and middle income groups. The recent research of National Family Health Survey (NFHS) reveals that 5.95% of rural women suffer from obesity (Goyal et al, 2009).
Fig. 1
CLASSIFICATION OF OBESITY

Pathogenesis

Exogenous obesity (impairment of central regulation of food intake)
(Landare, 1986)

Endogenous obesity (overeating due to abnormal fat (or) carbohydrate metabolism)

Body weight
• Mild
• Moderate
• Severe
• Very severe
(Thomas, 1996)

Body fat Distribution

Android (fat deposited in abdomen and trunk associated with increased risk of CVD, hypertension etc.)
(King 1992)

Gynecoid (fat accumulated in hips and lower abdomen)

Number and size of adipose cells

Hypertrophic (increase in size of fat cells)
(Whitney, 2002)

Hyperplastic (increase in number of fat cells)

Onset of Obesity

Adult-onset (Late onset) (enlargement of normal number of fat cells)

BMI
• Grade I
• Grade II
• Grade III
(Nisha, 2006)

Juvenile onset (Early onset) (abnormally large number of fat cells are present)
(Ensminger, 1995)
2.4 DIAGNOSIS OF OBESITY

Various methods are employed for diagnosing the extent of obesity to predict health risk.

2.4.1 Using body weight

<table>
<thead>
<tr>
<th>% body weight excess of normal</th>
<th>Degree of obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>mild</td>
</tr>
<tr>
<td>50</td>
<td>moderate</td>
</tr>
<tr>
<td>75</td>
<td>severe</td>
</tr>
<tr>
<td>100</td>
<td>very severe</td>
</tr>
</tbody>
</table>

(Thomas, 1996)

2.4.2 Using weight for height

In humans, the most common statistical estimate of obesity is the Body mass index (BMI), calculated by dividing the weight by the height squared; its unit is therefore Kg/m².

Body mass index (BMI): \[
\frac{\text{Weight (kg)}}{\text{Height (m²)}}
\]

(Thomas, 1996).

Table 2.4.2

Classification of obesity based on BMI and their associated health risk.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
<th>Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Grade I obesity</td>
<td>25.0-29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Grade II obesity</td>
<td>30.0-39.9</td>
<td>High to very high</td>
</tr>
<tr>
<td>Grade III obesity</td>
<td>&gt;40</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

(Myers, 2000)
Grade I obesity

These people have a BMI more than 25 but less than 29.9. Overweight does not affect their health; they have a normal health and life expectancy is above normal. They may reduce on their own (Thomas, 1996).

Grade II obesity

These people have a BMI more than 30 and less than 39.9. These patients should be treated by doctors and dietitians. Although they appear in good health, they have reduced tolerance to exercise with shortness of breath on exertion and they are unduly fatigued (Thomas, 1996).

Grade III obesity

The Body Mass Index is above 40, and these patients are in pathetic condition. They are susceptible to atherosclerosis, prone to accidents, have serious psychological disturbances (Thomas, 1996).

Interpretation of BMI

A person with a BMI more than 25 kg/m2 is considered overweight.

A BMI over 30 kg/m2 denotes obesity.

A further threshold at 40 kg/m2 is identified as urgent morbidity risk (morbid obesity) (Nisha, 2006).

BMI limit for Indians is:

Less than 18.4 - Underweight

18.5 - 22.9 - Normal

23 - 24.9 - Overweight

More than 25 – Obese (Health Ministry of India, 2008).

BMI is internationally accepted as a means of identifying overweight and obesity. Mortality increases gradually above a BMI of 25 kg/m2 with a sharper increase above a BMI of 30 kg/m2 (Schills, 2006). The World Health Organization has revised the BMI cut off for Asian Indians and suggested a BMI of 25 kg/m2 to define obesity against the 30 kg/m2 recommended for Europeans (WHO, 2000). Mortality was higher for women in the highest BMI quartiles (>27.7 kg/m2) (Maru, 2004).
2.4.3 Using body fat distribution

Fat distribution can be assessed by measuring the waist and hip circumference (Wardlaw et al, 1993).

**Waist to hip circumference**

\[
\frac{\text{waist circumference}}{\text{hip circumference}}
\]

Normal ratio = 0.7 \quad (Williams et al, 1990).

The cut-off used for WHR were >0.9 for males and >0.8 for females (Webb, 2002). A waist to hip circumference ratio of 0.95 (or) more for men and 0.85 (or) more for women indicates central obesity (apple-shaped) and an increased risk of obesity related disease (Bender, 2002).

**Waist circumference**

It is highly correlated with the amount of intra abdominal (or) visceral fat, which in many is an independent predictor of increased risk for diabetes, hypertension, dyslipidemia and ischemic heart disease (Schills, 2006).

The cut-offs for waist circumstances will be 90 cm for Indian men (as opposed to 102 cm globally) and 80 cm for Indian women (as opposed to 88 cm at the international level) (Health Ministry of India, 2008).

Measurement of abdominal obesity is strongly associated with increased cardiometabolic risk, cardiovascular events and mortality. Although waist circumference is a crude measurement, it correlates with obesity and visceral fat amount and is a surrogate marker for insulin resistance (Abramof, 2008).

Abdominal adiposity assessed using waist circumference is considered to be more appropriate to predict metabolic disorders than generalized adiposity assessed by BMI. Further Indians also tend to have excess body fat, abdominal and truncal adiposity. For any given waist circumference, they have increased body fat accumulation and for any given body fat, they have increased insulin resistance. These features have been referred to as the Asian Indian phenotype (or) paradox (Mohan and Deepa, 2006).

The study indicates a geographical variation in obesity parameters and its association with metabolic abnormalities. Such regional variations have also been
documented in the prevalence of diabetes and coronary artery disease (Mohan and Deepa, 2006). Persons with a normal BMI but a large waist circumference had a higher mortality risk, and hence increased waist circumference should be considered a risk factor for mortality, in addition to BMI (Koster, 2008). General adiposity and abdominal adiposity are associated with the risk of death and supports the use of waist circumference (or) waist to hip ratio in addition to BMI in assessing the risk of death (Pischon, 2008).

2.4.4 Using body fat

A variety of methods can be used to determine how much fat a person contains. The most widely used method measures skin fold thickness. Over half of body fat lies directly under the skin. The amount of fat under the skin in turn reflects the fat composition of the body (Nisha, 2006).

Skin fold thickness

The skin fold thickness can be taken on different trunk sites (subscapular, thigh, mid-calf). The skin fold at triceps is more reliable than at sub-scapular skin fold in the assessment of obesity (Birmingham, et al, 1993). A pinch of skin is precisely measured to determine the thickness of the subcutaneous fat layer (Nisha, 2006).

Triceps skin fold

Measurement is made on dorsal side at the mid- point between tip of the acromion of scapula and the tip of the Dacron on fore arm bone using harpender calipers. The tip of the skin fold caliper should be applied at the midpoint at a depth equal to the skin fold. Average of two measurements should be taken (Visweswara rao, 1995). Measurements greater than 18.6mm in men and 25.1mm in women indicate obesity (Sullivan, 1989).

2.5 MECHANISMS INVOLVED IN BODY WEIGHT REGULATION

Obesity is linked to altered function of the brain system and hypothalamus and to changes in the ANS, which regulates energy expenditure and regulates thermogenesis. At the molecular level altered production of neurotransmitters, chemical peptides and hormones may alter critical control and feedback mechanisms that maintain body weight (Ronzio, 2004).
Fig 2

Feedback mechanism involved in regulating food intake and weight.

Energy intake

Regulatory systems such as neurochemicals body fat stores, protein mass, hormones and post ingestion factors all play a role in regulating intake and weight. Many hormones and peptides derived both from the periphery and CNS (central nervous system), appear to be involved in food intake, regulatory system (Schills, 2006).

Norepinephrine and dopamine are released by SNS in response to dietary intake. Fasting and semi-starvation decrease SNS activity and increase adrenal medullary activity, increasing epinephrine levels which foster substrate mobilization (Vaselli and Maggio, 1998). Decrease in serotonin and increase in neuropeptide Y (NPY) increases during food deprivation, it may lead to an increase in appetite after dieting. Preferences and cravings for sweet, high fat foods observed among obese people may involve the endorphin system (Drewnowski et al, 1992). Cortico- tropin-releasing factor (CRF) is a potent anorexic agent. It decreases food intake and weakens the feeding response produced by norepinephrine and neuropeptide Y. CRF is released during exercise, starvation and its level is also increased in depressed patients. (Morley et al, 1992).

Cholecystokinin (CCK) is released by the intestinal tract when fats and proteins reach the small intestine. Receptors for CCK have been found in the GI tract and in the brain. At the brain level, CCK inhibits food intake. Bombesin,
reduces food intake and enhances the release of CCK. Enterostatin is involved specifically with the satiety following the consumption of fat. Apolipoprotein A- IV enters CNS and suppresses food consumption (Mahan, 2004).

Insulin acts in CNS to inhibit intake, and in peripheral nervous system facilitates synthesis and storage of fat. Impaired insulin activity reduces SNS activity, and impairs thermogenesis (Pi-sunyer et al, 1994).

A decrease in triiodothyronine lowers the response to SNS activity and diminishes adaptive thermogenesis. Such defect could be one of the factors predisposing some obese persons to excessive weight gain (Weinsier et al 2000).

PYY3-36, a member of Neuropeptide Y’ secreted by endocrine cells lining small bowel and colon appears to work in the hypothalamus, binding to a receptor and inhibiting neuropeptide Y production, which produces appetite decreasing peptides (Batterham et al, 2002).

Leptin is a hormone secreted by the adipose tissue that is correlated with the percent body fat. Animal studies established the involvement of leptin in increasing satiety and energy expenditure (Flier and Maratos – Flier ,1998) Energy restriction reduces leptin level and has been found to coincide with self-reported hunger, desire to eat, and prospective consumption. Hence, it regulates appetite (Keim et al,1998).

Ghrelin, a hormone produced primarily by the stomach, acts on hypothalamus to stimulate feeding and on other tissues to slow metabolism and reduce fat oxidation (Cummings et al, 2002).

Leptin and ghrelin are considered to be complementary in their influence on appetite with the stomach producing ghrelin when relatively empty and leptin being produced by adipose tissue when satiated with nutrients (Nisha, 2006).

**Energy expenditure**

The components of total energy expenditure (TEE), are the resting energy expenditure (REE), energy expended in voluntary activity and thermogenic effect of food. TEF (thermogenic effect of food) is the increase in
energy expenditure associated with digestion, absorption and storage of macro nutrients usually account to 7% to 10% (Schills, 2006). Meal size, meal composition, the nature of the previous diet, insulin resistance, physical activity and aging influence TEF (Dejong and Bray, 1997).

When the body is suddenly deprived of adequate energy, the RMR adapts to conserve energy by as much as 15% in 2 weeks. When adequate food intake is restored, RMR returns to baseline levels (Ravussin and Swinburn, 1997). REE is the energy required to maintain basic physiological functions which comprises 60 to 80% of TEE (Schills, 2006).

Energy expended in voluntary activity (or) physical activity related energy expenditure (PAEE) accounts for 15 to 30% of total energy expenditure (McArdle, 1999).

2.6 ETIOLOGY OF OBESITY

Obesity involves complex etiological links between the genetic, metabolic and neural frameworks on one hand and behavior, food habits, physical activity and socio-cultural factors on the other (Nammi et al, 2004).

2.6.1 Genetic considerations

Studies of twins yield similar findings; identical twins are twice as likely to weigh the same as fraternal twins – even when reared apart. These findings suggest an important role of genetics in determining a person’s susceptibility to obesity. In other words genes may not cause obesity but genetic factor may influence the food intake activity patterns that lead to it and the metabolic pathway that maintain it. Gene ‘ob’ causes fat cells to produce a satiety protein called leptin (Schills, 2006). The leptin receptors are concentrated in hypothalamus. Any mutation of ‘ob’ gene leads to improper coding of leptin, which results in obesity.

Family exerts social pressure and teaches children, habits and attitudes towards food. Melanocortin-4-receptor gene (MC4R) mutations have been the cause for more than 4% of patients with severe obesity. Defects in proliferator activator-γ receptor (fat cell differentiation and proliferation) cause modest obesity. Leptin
receptor mutation is also one of the causes. Genes can affect energy intake, energy expenditure and storage efficiency (Schills, 2006).

2.6.2 Dietary factors

Excessive dietary carbohydrate, particularly when it is a form which is rapidly digested and readily absorbed is the strongest stimulator of the secretion of insulin, the hormone that promotes the synthesis and storage of fat. Concentrated sources of fat such as butter, cream, margarine and vegetable oils, which may be eaten separately (or) combined with cereals in excess may contribute to obesity. High fat diet contribute to low bulk, which may allow some people to consume excessive calories before satiety is achieved. Test feedings consisting of lean meat were potent stimulators of the copious secretion of the growth hormone, as an agent favouring the development of obesity in growing children (Cataldo et al, 1995).

Research has shown that eating 2 (or) 3 large meals per day is more likely to result in excessive fattening (Whitney, 2002). Eating fewer meals may increase fat deposition while smaller more frequent meals with more food at breakfast and less at supper, may promote weight loss (Ronzio, 2004).

Heavy use of the seasoning agents like garlic, onions, mustard may make food highly palatable and increase the flow of digestive juices and generally promote over eating. It has often been noted that many obese people appear to eat their food more rapidly than the non-obese people (Ensminger, 1995). Overeating is more likely to occur when the forms and types of food are high in calories, low in fibre and do not require much chewing for E.g., mashed potatoes (Thomas, 1996). Lack of fibre leads to decreased satiety, increased consumption of energy dense food and diminished chewing (Mahan, 2004).

Fast food plays a major role in the development of obesity. Increasing number of two income households, when both parents work, there is an increase in number of restaurants and takeout meals (Kant et al, 2000). It is often high in fat and a high fat diet promotes obesity. Data from NHANES-III
suggest that intake of energy dense, nutrient-poor foods, result in an increased risk of overeating (Kant et al, 2000). Excessive TV watching correlates with overeating (Ronzio, 2004). Using new research methods the investigators have observed that obese people generally eat more, but they habitually under report their food consumption (Ronzio, 2004). Restrained eating, reports more food cravings and binge eating. (Antia, 2006).

2.6.3 Physical inactivity

Modern technology has replaced physical activity at home, at work and in transportation. Inactivity contributes to weight gain and poor health. In turn, television watching may contribute mostly to physical inactivity. A study by a team at Peninsula Medical school, in Plymouth suggests that the obesity epidemic is caused more by eating too much than how much activity you do (Bender, 2002). Greater percentage of population spend their entire workday behind desk (or) computer, seeing virtually no exercise. In kitchen, the microwave oven has seen sales of unhealthy frozen convenience foods and has encouraged more elaborate snacking (Nisha, 2006)

2.6.4 Psychological factors

Fat persons are perceived as having less control over their appetite as being more responsive to external cues than to internal ones (Williams, 1998). Overeating may be a compensatory mechanism for failure or frustrations in life. A housewife is more exposed to food and more likely to be obese than a women working outdoors (Antia, 2006).

2.6.5 Social factors

In a Finland study, high parity was found to be associated with high weight gain among women of low educational level, but with low weight gain in women of high educational level (Desai, 2000). Another study finds women who married into higher status are predictably thinner than those married to lower status (Nisha, 2006).
2.6.6 Physiologic factors

Brown fat (specialized adipose tissue) burns off excess energy as heat, at a higher rate than white fat cells. Obesity results when some sort of brown tissue defect interfere with this function (Williams, 1998). In animals, defective heat production in brown fat leads to obesity, but effective heat production permits leanness despite over-eating (Caterson, 1997).

Obesity occurs in case of excess corticosteroids (Cushing’s syndrome), insulin excess, alterations in the level of progesterone (or) oestrogen (Stein leventhal syndrome) (Whitney, 2002)

Muscular people have a higher BMR. Muscle burns about three times more calories than fat. Around 0.25 kg of muscle every year is lost after your late twenties. Hence, BMR drops about 2% each decade and body burns fewer calories (Bean, 2009).

2.7 COMPLICATIONS OF OBESITY

Obesity has been directly linked with mortality and many chronic ailments. (NIH, 1998). Chronic diseases such as heart disease, type 2 diabetes, hypertension, stroke, gall bladder disease, sleep apnoea, certain cancers and osteoarthritis are associated with obesity and tend to worsen as the degree of obesity increases (American obesity association, 2001).

Women are vulnerable to several weight related health risks associated with being overweight. They have shorter life expectancy, high maternal mortality and higher incidence of chronic diseases and conditions such as obesity, osteoporosis, diabetes, hypertension and other cardiovascular diseases. Obese women have higher rates of cancer of the uterus, gall bladder, ovary and breast, increased waist to hip ratio, increased risk of breast cancer (Antia, 2006).

Regional patterns of fat deposit are controlled genetically and differ between men and women. Abdominal fat (or) visceral fat component (android type) common among men is strongly correlated with risk factors such as glucose intolerance, hyperlipidemia and hypertension (Matsuzawa et al, 1994). Excess luteofemoral fat (gynecoid) distribution common in women do not develop the impairments of glucose metabolism seen in obese women of the same weight with abdominal fat. Post- menopausal women more closely follow the male pattern of abdominal fat store. As a result these women have an increased risk for blood glucose, lipid and pressure abnormalities (Dietz, 1998).
Central obesity (waist predominant (or) male-type obesity) is an important risk factor for the metabolic syndrome (syndrome x) the clustering of many diseases and risk factors that heavily predispose for cardiovascular disease. These are diabetes mellitus, high blood pressure, high blood cholesterol and triglyceride levels (combined hyperlipidemia) (Anderson et al, 2007).

**Table 2.7**

Complications associated with obesity

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>congestive heart failure, enlarged heart and its associated arrhythmia and dizziness, cor pulmonale, varicose veins and pulmonary embolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>polycystic ovarian syndrome (PCOS), menstrual disorders and infertility.</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>gastroesophageal reflux disease (GERD), fatty liver diseases, cholelithiasis (gallstones), hernia and colorectal cancer.</td>
</tr>
<tr>
<td>Renal and Genitourinary</td>
<td>Urinary incontinence, glomerulopathy, hypogonadism (male), breast cancer (female), uterine cancer (female), stillbirth.</td>
</tr>
<tr>
<td>Integument</td>
<td>(skin and appendages); stretch marks, acanthosis nigricans, lymphedema, cellulitis, carbuncles, intertrigo.</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>hyperuricemia (which predisposes to gout), immobility, osteoarthritis, low back pain.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>stroke, meralgia paresthetica, headache, carpal tunnel syndrome, dementia.</td>
</tr>
<tr>
<td>Respiratory</td>
<td>dyspnea, obstructive sleep apnea, hypoventilation syndrome, Pickwickian Syndrome, asthma.</td>
</tr>
<tr>
<td>Psychological</td>
<td>Depression, low self esteem, body image disorder, social stigmatization.</td>
</tr>
</tbody>
</table>

(Nisha, 2006)
2.7.1 **Physical disability**

Dietary fat contributes to the most common form of osteoarthritis, because excess weight subjects the major joints to extra wear and tear (Myers, 2000). A high-fat diet appears to increase risk of rheumatoid arthritis (RA), the most serious and potentially crippling form of joint disease. Several studies suggest that a low-fat diet relieves RA symptoms (Myers, 2000).

2.7.2 **Metabolic disorders**

Gall bladder disease is the most common gastro-intestinal disorder in obese individuals, because the bile of obese people is supersaturated with cholesterol and hence liable to form gall stones. Obese women have a 2.7 fold increase in the prevalence of gall bladder disease. There is an increased risk of gallstones in individuals having BMI of 20kg/m² (or) more (Gregory, 1990).

There is a consistent graded relationship between increased BMI and prevalence of NIDDM (Non-insulin dependent diabetes mellitus) and insulin resistance. BMI above 35 kg/m² increases the risk by 93 fold in women and by 42 fold in men. Non-insulin dependent diabetes mellitus (NIDDM) is an important contributor to morbidity and mortality in obese people (Garrow, 1993).

Gout is usually accompanied by elevated blood levels of urates, which may sometimes be caused by crash diet, low in carbohydrates, but high in fat and proteins. The higher rate of kidney disease in heavy people may stem from obesity (Maurice, 1992). Metabolic syndrome may have an independent effect on health related quality of life in obese individuals (Tsai, 2008).

2.7.3 **Respiratory disease**

Winter coughing and bronchitis is common among obese individuals because of fat surrounding the diaphragm (Peggy, 1994). An increased amount of fat in the chest wall and abdomen limits respiratory expansion reduces lung volume, results in hypoventilation syndrome. Sleep apnoea is stoppage of breathing during sleep; it is associated with fatal irregular heartbeats and high mortality (Feldman et al, 1985).
2.7.4 Malignancies

Obese women have higher incidence of endometrial, ovarian, cervical and post-menopausal breast cancer, while obese men have incidents of prostate cancer. A positive relationship between cancer and BMI was observed (Feldman, 2000).

2.7.5 Obstetrical complications

Obese women have a higher risk of caesarean delivery due to variety of foetal size. They are more susceptible to toxaemia of pregnancy and experience difficult pregnancies and their infants are likely to suffer fatal distress. There is also higher still born rate among obese women (Peggy, 1994).

2.7.6 Psychological disturbance

Obese people, particularly those who have made many attempts to lose weight, often have lower self-esteem (Caterson, 1997). Obese people (10 to 15%) had reported moderate (or) severe depression. Severely obese women (30%) report significant depression (Schills, 2006).

2.8 OBESITY IN RELATION TO CARDIOVASCULAR DISEASE (CVD) AND LIPOPROTEIN PROFILE

Obesity puts strain on organs including heart. Having a BMI greater than 25 greatly increases the chance of developing diabetes, high blood cholesterol and high blood pressure; which are risk factors of heart disease (Ryan et al, 2001). BMI and Coronary heart disease (CHD) are positively related. As BMI goes up the risk of CHD also increases (NCHS, 2002). The Veterans administration normative aging study also showed that weight change in both men and women was significantly related to change in CVD risk factors (Desai, 2000). The increased risk of CVD is twofold in women of BMI 25-28.9kg/m2 and 3.6 fold for BMI in 29 kg/m2 (or) more (Nammi et al, 2004).

Postmenopausal Asian women are at a high risk for development of cardiovascular disease. Women who display central (or) truncal obesity, with waist circumference (WC) of 40 inches (100 CM) (or) above are at increased cardiovascular risk compared to those with lower body obesity (Pouliat et al, 1994). Excess fat around the waist especially for women with a WHR greater than 0.8 results in additional risk for CVD (Ryan, 2001).
Risk factors for heart disease include age, family history, abnormal cholesterol, diabetes mellitus, obesity, life style (including diet, physical activity, psychosocial factors, alcohol, high homocysteine and elevated C-reactive protein) (NIH, 2000). Physical inactivity (or) a low level of fitness is an independent risk factor for CHD (Schoenborn and Barnes, 2002). Important risk factors like insulin resistance, CRP and low HDL levels are not interrelated and may contribute independently to cardiovascular risk (Wasir et al, 2007). The higher prevalence of cardiovascular disease in obese individuals is indirectly mediated, to a large extent, by the increased frequency of various well known risk factors like hypertension, diabetes, and dyslipidemia, either individually or as part of the metabolic syndrome (Mathew, 2008).

Relation to lipid metabolism

Large-scale studies have demonstrated a definite relationship between amount of fat, type of dietary fat and elevated blood lipid levels, especially cholesterol. Elevated blood cholesterol has been shown to be a primary key to the development of atherosclerosis (Mensink et al, 2003).

Blood lipids are transported in the blood bound to proteins. These complex particles, called lipoproteins vary in composition, size and density. The five classes of lipoproteins- chylomicrons, VLDL, IDL, and LDL AND HDL consist of varying amount of triglyceride, cholesterol, phospholipid and protein (Whitney, 2002).

Lipoprotein profile

A standard lipoprotein profile includes measurement of total cholesterol, LDL, HDL and triglycerides levels after fasting. Lipid profile must be taken in the fasting state (8 to 12 hours after eating), to allow time for chylomicrons to clear (NCEP, 2001).

The total cholesterol and triglyceride level can be determined directly on fasting serum. HDL is determined on the supernatant after precipitation of apolipoprotein B containing lipoprotein (VLDL and LDL). LDL cholesterol indirectly calculated by equation;

\[
\text{LDL cholesterol} = \text{Total cholesterol} - \text{HDL cholesterol} - \left( \frac{\text{Triglyceride}}{5} \right)
\]

(Friedwald formula).

The equation hold for triglyceride levels up to but not above 400mg /dl) (NCEP, 2001)
### Table 2.8 (a)

**Characteristics and Functions of the Plasma Lipoproteins**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chylomicron</th>
<th>VLDL</th>
<th>IDL</th>
<th>LDL</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density g/ml</td>
<td>&lt;0.95</td>
<td>0.95-1.006</td>
<td>1.006-1.019</td>
<td>1.019-1.063</td>
<td>1.063-1.210</td>
</tr>
<tr>
<td>Electrophoretic mobility</td>
<td>Pre-beta</td>
<td>Pre-beta to beta</td>
<td>Beta</td>
<td>Alpha</td>
<td></td>
</tr>
<tr>
<td>Origin</td>
<td>liver and intestine</td>
<td>In circulation secondary to catabolism of other lipoproteins</td>
<td>liver</td>
<td>Liver and intestine</td>
<td></td>
</tr>
<tr>
<td>Physiologic role</td>
<td>Transport of dietary triglyceride</td>
<td>Transport of endogeneous triglyceride</td>
<td>LDL Precursor</td>
<td>Major Cholesterol transport lipoprotein</td>
<td>Reverse cholesterol transport</td>
</tr>
<tr>
<td>Relative atherogenicity</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>Negatively correlated with atherosclerosis</td>
</tr>
</tbody>
</table>

#### Composition (%)

<table>
<thead>
<tr>
<th></th>
<th>Triglyceride</th>
<th>Cholesterol</th>
<th>Phospholipid</th>
<th>Protein</th>
<th>Major apolipoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>A-I</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>10</td>
<td>18</td>
<td>10</td>
<td>Beta 100</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>Beta 100</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>50</td>
<td>15</td>
<td>25</td>
<td>Beta 100</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>20</td>
<td>25</td>
<td>50</td>
<td>A-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A-IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B-48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-II</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>E</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-III</td>
</tr>
</tbody>
</table>

|                  | Size in nanometer (nm) | 75-100 | 30-80 | 25-40 | 10-20 | 7.5-10 |

|                  | Size, density Description | Largest, lightest | Next largest, lightest | Intermediate Size & lighter | Smaller, heavier | Smallest, most dense, heaviest |

(Mahan, 2004)
Table 2.8 (b)
Relationship between lipoprotein fractions and CHD risk

Desirable Range for Assessment of Risk for Cardiovascular Disease

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Desirable Range (mg/dl)</th>
<th>Border line range (mg/dl)</th>
<th>Risk Range (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>&lt;200</td>
<td>200-249</td>
<td>&gt;250</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;130</td>
<td>130-159</td>
<td>&gt;160</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;45</td>
<td>35-45</td>
<td>&lt;35</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&lt;150</td>
<td>150-200</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

(Theodore, 1996)

A woman with a serum cholesterol level of greater than 260mg/dl has a relative risk for CHD compared to a woman with a cholesterol < 200mg/dl (Bass et al, 1993). High concentrations of VLDL remnants and IDL have been directly related to lesion progression and subsequent coronary events in men and women (NCEP 2001). High levels of VLDL confer a significant risk to both genders, but appear to be more important risk factor for women (Roeters et al, 2002). LDL is the major atherogenic lipoprotein in women. The higher the levels, the higher the CHD risk. Many population studies have shown that HDL cholesterol is a strong negative, independent predictor of CHD incidence and mortality in men and women (Martinez et al, 2004). Elevated triglyceride levels have been shown to be an independent risk factor for CHD in women (Castelli, 1987). For women, low HDL and increased triglycerides are strong risk predictors than in men. In women, higher BMI’s are associated with triglyceride levels that are 35 to 45 mg/dl higher than average and HDL Cholesterol levels that are 5 to 9 mg/dl lower than average. The risk for IHD in women increases when HDL levels are less than 45 mg/dl (Martinez et al, 2004).

Physical inactivity seems to have an independent effect on CVD risks whereas obesity increases the risk partly through the modification of other risk factors (Hu, 2004).

2.9 OBESITY, HYPERTENSION AND CORONARY HEART DISEASE (CHD)

Hypertension is a risk factor for CHD, stroke and congestive heart failure. Hypertension contributes to disease development by causing vascular injury and stress to the myocardium (AHA, 1999). Systolic and Diastolic hypertension,
defined as BP of more than 140/90 mm Hg, strongly and independently increases the risk of CHD in women (JNC-VI, 1997).

Hypertension is prevalent in obese adults at a rate of 2.9 fold than non-obese population and weight reduction reduces risk of developing hypertension. There is a definite independent association between hypertension and obesity. The Nurses’ health study, (NHS) showed that those women with BMI greater than 31 had a risk rate of 6.3% of developing high blood pressure. In addition, an increase in weight of 1Kg was associated with a 12% increased risk of developing hypertension (Mahan, 2004).

An increase in BP is closely correlated with an increase in BMI. The prevalence of high BP in person with a BMI greater than 30 is 32% for women compared to 17% for women with a normal BMI (<25) (NIH,1998). In the Framingham study, an increase in relative weight of 10% was predictive of a rise in BP of 7mm Hg (Mahan, 2004).

As women, age, their hypertension, is associated with increased peripheral resistance, low (or) normal plasma volume and low plasma rennin levels. Some of the physiologic changes proposed to explain the relationship between excess body weight and BP are insulin resistance, activation of SNS, hyperinsulinemia and renin-angiotensin systems and physical changes in kidney (Hall, 1994).

Giampaoli and Vanuzzo (2002), observed that prevalence of hypertension increased with increasing age. The change was particularly marked after menopause. Staessen et al (1997), Kawada (2002) and Raskin (2004), stated that menopause was accompanied by a steeper rise in systolic blood pressure with age and diastolic blood pressure was independent of age. BMI had a positive significant (P<0.01) association with SBP and DBP. Huang et al (1998), reported that higher BMI at post-menopausal stage strongly increased the risk of developing hypertension. Daniel et al (1999), reported that a greater deposition of central fat is correlated with blood pressure. Ishikawa (2002), reported that BMI increased, beyond 22kg/m2 was related to an increased risk for hypertension.

2.10 OBESITY, CORONARY HEART DISEASE (CHD) AND MENOPAUSE

Woman, progress through many phases during reproductive life and menopause is an entirely expected normal process. The word menopause was first
used by physicians in 1821 (Ballard, 2003). The Greek origins are, menos, which means month and pauses, which means ending. Menopause is therefore the cessation of the monthly menstrual cycle. The mean age of women at menopause is 51 years, but range in between 40 and 55 years of age (Wilson, 2002).

Menopause actually refers to only one day in your life, the 365th day from the date of your last period. Post menopause is the time after menopause. Increased rates of heart disease, osteoporosis, type 2 diabetes, obesity, Alzheimer’s, high BP, high cholesterol are noted in the post-menopausal years (Rossouw et al, 2002).

CHD is the leading cause of death for women in US (over 53% postmenopausal will die of CVD). The incidence of CVD increases markedly after menopause. It also increases steeply after menopause (NIH, 2000).

Oestrogen suppresses appetite, hence appetite increases when its production is reduced (after menopause). Oestrogen lowers the LDL level by 15 to 19%, by increasing clearance of LDL from circulation. It raises HDL by 5% only (Mathews et al, 2008). It suppressed the uptake of LDL by blood vessel walls, impairing the development of endothelial atheroma (Wagner et al, 1997), and promoted vasodilation (William, 1998). Oestrogen bind to endothelial oestrogen receptors which stimulate the release of nitric oxide (endogenous vasodilator) (Hayashi et al, 1992). Vasodilation may also be due to oestrogen induced increase in prostacyclin (vasodilator) and decrease in β thromboxane (vasoconstrictor).It also retards the oxidation of LDL and decreases atherogenicity (Sack et al, 1994).

Lipid levels have a higher predictive value in post-menopausal women than in pre-menopausal women. Post-menopausal women, who are at increased risk for CHD have a greater prevalence of smaller LDL which is predictive of CHD risk in both men and women (Campos et al, 1992). During the menopausal period, TC, LDL and TG levels increase and HDL level decrease, especially in women who gain weight (Krummel et al, 1993).

Postmenopausal women stand at a crossroad facing the possibility of living the remainder of their lives in essentially good health (or) facing the probable onset of chronic diseases. Obesity can lead to an aggravated risk of heart disease, hypertension, diabetes, sleep apnoea, cancer, osteoarthritis and mental health problems (Dennis, 2007). Post-menopausal women are at an age when the incidence and exacerbation of chronic health conditions associated with obesity becomes more prevalent (Dennis, 2007).
Menopausal transition is characterized by ovarian failure and its consequent decrease in female sex steroid production. Post-menopausal women seem to have less lean body mass (LBM) compared with premenopausal women (Sipila, 2003).

Women face various psychological as well as physiological changes in the menopausal stage. There is a tendency to put weight after menopause, which is a predisposing factor for several other chronic disease like CVD, hypertension etc. Seventy percent of women age 45-54 years, are overweight or obese (Evans, 2002).

Obesity is recognized as an independent risk factor for hypertension, lipid abnormalities and diabetes mellitus, which are known to be independent risk factors for CVD (Zodpey 1994; Ganguly et al, 1997). Cardiovascular disease is the leading cause of death in women who have past the age of menopause (Upkar, 2000). Chandha (2001), also reported that majority of women, less than 65 years of age die of cardiovascular disease. Kawada (2002), reported that BMI has an influence on blood pressure and lipid profile and is a good predictor of hypertension and hyperlipidemia.

The waist to hip ratio (WHR) showed significant positive association with systolic and diastolic blood pressures but not with lipid variables in one of the rural population (Gupta and Majumdar, 1994). Sensitivity of waist circumference is an index of disease risk in post menopausal women (Pelt et al, 2001). The body fat distribution changes according to menopausal status, with central obesity were more pronounced in post menopausal women (Garauet, 2002).

Although with aging systolic blood pressure increase for both genders, in women the rate of increase is much slower in younger adult and more rapid after menopause (Canoy et al, 2004).

2.11 MANAGEMENT OF OBESITY

Management include both weight control (or) reducing excess body weight and maintaining that weight loss, as well as, initiating other measures to control associated risk factors. Periodic evaluation for obesity should be done by the measurement of BMI, measurement of waist circumference etc., to assess risk factors. Based on the evaluation, appropriate treatment can be suggested (Mahan, 2004).
People with BMI 25 – 29.9, without any comorbidities are encouraged to prevent weight gain. People with BMI 25 – 29.9 with two or more risk factors are encouraged to induce a lifestyle modification through tripartite approach (Diet, behavior therapy and exercise). Pharmacotherapy with lifestyle modification is recommended for people with BMI 30 and BMI above 27 with co-morbid condition. Bariatric surgery is done for people with BMI >40 (or) BMI >35 with comorbidities (Mahan, 2004).

**FIG -3**

Management of Obesity

<table>
<thead>
<tr>
<th>OBESITY / OVERWEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess energy intake</td>
</tr>
<tr>
<td>Inadequate physical activity</td>
</tr>
</tbody>
</table>

**CLASSIFICATION OF OBESITY**
- BMI >25
- Excess body mass (% fat)
- Android vs. gynoid fat distribution

**ASSOCIATED CHRONIC DISORDERS (Syndrome X)**
- Glucose intolerance
- Insulin resistance
- Hyperlipidemia
- Hypertension

**MEDICAL MANAGEMENT**
- Lifestyle modification (increased exercise)
- Psychological support
- Drugs, Surgery

**NUTRITIONAL MANAGEMENT**
- Food choice changes
- Nutrition education
- Maintain Micronutrient intake

(Anderson and Garner, 2001)
2.11.1 Lifestyle Modification

Lifestyle modification programme for prevention and treatment of adult onset obesity currently focus on reducing situational and emotional overeating; the results of this study suggests that a stronger emphasis on strategies that target habitual overeating may be warranted (Hays, 2008). Adherence to healthy lifestyle behaviours was associated with a lower risk even among obese individuals (Jensen et al, 2008).

2.11.2 Diet therapy

Restrictions of calories represent the first line therapy in all cases except in pregnancy, lactation, terminal illness, anorexia nervosa, cholelithiasis and osteoporosis. Schlordt and colleagues found that patients who were instructed to eat 25g / day of fat with ad libidum intake of CHO lost 4.6Kg in 20 weeks, compared to a significantly greater loss of 8.8 kg for patients, who prescribed the same fat goal as a part of a 1200 K cal to 1000 K calories/day diet (Schills, 2006). Low carbohydrate and high protein diet (Atkins diet), is meant for short term use (Schills,2006). Extreme energy restricted diet provides fewer than 800 K calories per day and starvation (or) fasting diets provide fewer than 200 K calories per day (Whitney,2002)

Fasting is seldom prescribed as a treatment. It is a drastic approach, as it leads to acidosis, postural hypotension, increased urinary loss of cations, increase in serum uric acid, constipation, a decrease in BMR, loss of heart-muscle and also leads to death (Antia, 2006). Starvation therapy has been used in hospital setting to treat seriously obese patients, especially those who are to undergo surgery. Vitamins, minerals and fluids are given and the obese person can lose at about 2.3kg/week if starved completely (Schills,2006)

It has been observed that calorie restriction alone has remarkable effects compared to exercise alone (Anderson et al, 1995). Meal replacement programmes and formula diets can be used as an effective tool in weight management (Ashley et al, 2001).
Eating small regular meal increase your metabolism and it burns off calories in a better way than one meal a day. In a crossover trial in a metabolic ward, when obese patients were fed 800kcals as either 1(or) 5 meals a day, the patient were much hungrier and lost more lean tissue on the one meal phase than on five meals a day (Desai, 2000).

According to research at the University of Florida, eating quickly means the satiety centre doesn’t receive right signals and hence the person feels hungrier. Leading a busy stressful life affects the eating pattern and breakfast skipping results in overeating. Overeating can be avoided if wider variety of foods is not offered and putting the left-over meals out of sight. Levels of hunger hormones increases in the day and may pose a desire for food in the evening. Eating large portions of salads (or) fruits as a starter will cut down the calories of main meals. Taking fruit juices (or) smoothies than fruits are less satiating (Glenville and Esson, 2004).

Breakfast kick starts your metabolism and allows you the whole day to burn up those calories. Breakfast stabilizes blood sugar levels, which regulates your energy levels and the risk of over eating (Schills, 2006).

2.11.3 Exercise

Increased exercise can result in an energy deficit and even without diet, exercise alone can be expected to lower weight around 2 to 3 kg, depending on the intensity, duration and type of exercise. It has been demonstrated that weight gain is significantly less likely to occur when physical activity is combined with any weight reduction method (Blaire et al, 2002).

Engaging in regular exercise helps to ensure continued success in maintaining weight loss rather than up and down effect of fad dieting (Rossenfeld, 2001). Exercise is extremely important and should be an integral part of a weight management program. By increasing LBM (lean body mass) in proportion to fat, exercise helps to balance the loss of LBM and reduction of Resting metabolic rate (RMR) that inevitably accompany even a well managed weight reduction program (Mahan, 2004).

Maintaining a regular exercise program can also help combat obesity, one of the risk factor for CVD. Aerobic exercise is valuable in fighting other risk factors for heart disease, which include favourable changes in
cholesterol levels as well as triglycerides (Brubaker, Kamineky and Whaley, 2002). Exercise also significantly lowers your risk of heart disease, stroke, diabetes and cancer. Regular exercise helps to reduce BP and blood cholesterol levels and also improves appetite control (Hu, 2004). Exercise improves the psychological well-being and thereby increases self esteem (Blaire et al, 2002).

Higher fitness reduces risk for cardiac mortality in women with heart disease (Kavanagh et al, 2003). Regular exercise prevents the development of high BP in women and improves blood pressure control in those with and without hypertension. BP lowering effect of exercise can last for up to 22 hours after endurance exercise and is greatest in those with the highest baseline BP (Pescatello et al, 2004).

In a study of 70 healthy female twins, total body fat and central abdominal fat were lower in women who reported vigorous weight-bearing activity (Samaras et al 1999). Each hour per day of brisk walking was associated with a 24% reduction in obesity and 34% reduction in type II diabetes. Physical activity protects against weight gain even if an individual is genetically predisposed to it (Blair et al, 2002). For every 2 hours spent more on watching TV, there was a 23% increase in obesity and 14% increase in type II diabetes (Hu, 2004).

Observational studies, have shown that regular physical activity in women lowers risk of CHD and stroke (Hu et al 2000; Manson et al 2002). 70,000 post-menopausal women were enrolled in Women’s Health Initiative observational study. In this investigation, women who sat for prolonged periods had a higher risk of cardiovascular events (Manson et al, 2002).

The mechanisms by which aerobic exercise reduce the risk of CVD and stroke include reduction in BP, improvement in lipid profile, reduction of inflammation in the blood vessel walls, treatment and prevention of type II diabetes mellitus and reduction in body weight. Participation in a regular exercise program clearly lowers BP in women with (or) without hypertension (Cox et al, 2001; Whelton et al, 2002).

Inflammation, (hs-CRP) clearly has a role in CVD. The best advice for women at this time is to control inflammation as well as other factors by maintaining an active life style with consistent exercise and eating a diet low in SFA and high in Soya nuts, fibre and plant sterol (Kettler et al, 2006).
2.11.4 Behaviour modification

Behaviour therapy is an useful adjunct, when incorporated into treatment for weight loss and weight maintenance. Patients need to be trained in gaining self-control of their eating habits. Behaviour modification programme which seek to eliminate improper eating behaviours (eating while watching TV, eating too rapidly, eating when not hungry etc) includes individual (or) group counseling of patients. Data indicates that patients, currently treated by a comprehensive group behavioural approach lost approximately 10.7 kg in 30 weeks of treatment (Nammi et al, 2004).

2.11.5 Pharmaceutical Management

Drug treatment is advised only for subjects with BMI >27 and with associated risk factor (or) with a BMI > 30 and thus at medical risk because of their obesity. It should not be used for cosmetic weight loss. Weight loss modification should be used only as an adjunct to dietary and exercise regimes coupled with a program of behavioural treatment and nutritional counseling (NHLBI, 1998).

Drugs act by suppressing appetite, (Noradrenergic agents) enhancing satiety (serotoenergic agents) inhibiting digestion and absorption of food nutrients by gut (antiabsorptive agents), blocking digestive enzymes and by increasing urine output of nutrients (Nammi et al, 2004).

In their search for weight loss, some consumers turn to natural herb products like St, John’s wort, ephedrine, cellasene, chitosan, conjugated linoleic acid and hydroxy citric acid (Nammi et al, 2004).

2.11.6 Surgery

Surgery is indicated when BMI is exceedingly high (>40 kg/m2 or >30 kg/m2 with obesity- related medical co-morbidities) and when other treatment modalities have failed. The most popular surgical procedures used for treatment of severe obesities involve gastric portioning or gastroplasty and gastric by-pass (Nammi et al, 2004).

Gastric and nutritional complications (Seeraha et al, 1996) may be serious implications of the surgery. Nutritional deficiencies and intractable vomiting are frequently associated with surgery. Surgical treatments for obesity resolve most
co-morbidities of severe obesity such as hypertension (Foley et al, 1992, Carson et al, 1994) serum lipid levels (Olsson et al, 1984) and diabetes mellitus (Herbst et al, 1984 and Pories et al, 1995).

Adherence to these interventions over long periods of time is challenging, hence researchers are seeking ways to promote weight loss by modifying dietary intake patterns. Both animal and human studies have proved that diet high in protein increases satiety, curbing the appetite and aiding in weight loss (Astrup, 2005).

2.12 SOYA, A SOURCE OF DIETARY PROTEIN AND OBESITY

Soyabees are the most economically important bean in the world. It is native to eastern Asia. The United States is the world leader in Soya bean production, growing about 2 billion bushals in annually more than 50% of the world crop. (Soyabean Encyclopaedia Brittanica 2009). Other major Soyabean producing nations are Brazil, Argentina, China, Paraguay, Canada and Bolivia [UN Food and Agriculture Organisation (FAO, 2006)].

Scientific classification of Soyabees

- Kingdom : Plantae
- Phylum : Magnoliophyta
- Class : Magnoliopsida
- Order : Fabales
- Family : Fabaceae
- Sub family : Faboidea
- Genus : Glycine
- Species : G. Max
- Binomial name : Glycine max.

The genus Glycine Wild is divided into two subgenera, Glycine and Soja. The subgenus Soja include the cultivated Soyabean, Glycine max and the wild Soyabean, Glycine soja (Sneller 2003).

2.12.1 Description and physical characteristics

Soyabees occur in various sizes and in many hull (or)seed coat colour including black, brown, blue, yellow, green and mottled. The tube of the mature bean is hard, water resistant and protects the cotyledon and germ from damage. Seeds contain very high levels of protein and can undergo

2.12.2 Nutritional facts of Soya bean

Soya is an inexpensive, high quality, vitamin and mineral rich, plant protein with lots of soluble fibre, plant based Omega 3 fatty acid; it offers a wealth of disease fighting phytonutrients and is the richest source of phytooestrogens. It plays a positive role in preventing CVD, cancer and osteoporosis as well as relieves menopausal and menstrual symptoms (Pratt and Mathews, 2004).

Soyabean comprise approximately 8% seed coat (or) hull, 90% cotyledons and 2% hypocotyls axis (or) germ. It contain about 20-25% Oil, 30-50% protein and 14-21 % CHO but little starch (Singh, 2002).

Soyabean protein is used as a meat substitute, its NPU is 65. Soya protein contain substantial amount of lysine. They are the only legume that contain the nine essential amino acids in the correct proportion for human health. Soya protein is therefore a high quality, complete protein. It is also a good source of phosphorus, potassium, B vitamins, Zinc, iron, and the anti-oxidant Vitamin E (Singh, 2002).

Soya protein is derived from Soyabean. Most studies have used Soya protein. These are either isolated (or) textured Soya protein. Soya protein contain heat labile, anti-nutritional components, including protease inhibitors, which must be eliminated by processing (Shun, 1997).

Most Soya protein is relatively heat stable storage protein. This heat stability enables Soya food products requiring high temperature cooking, such as tofu, Soya milk and textured vegetable protein(Soya flour) to be made (Shun, 1997).

The principal soluble carbohydrates of mature Soya beans are sucrose (2.5-8.2%), raffinose(0.1-10%), stachyose (1.4 to 4.1%). Raffinose and stachyose are not digestible and hence contribute to flatulence and abdominal discomfort in humans and other monogastric animals. On the other hand, they encourage the growth of indigenous bifidobacteria in the colon against putrefactive bacteria. The insoluble carbohydrates in Soya beans consists of complex polysaccharides like cellulose, hemicellulose and pectin (Blackman et al, 1992).
2.12.3 Benefits of Soya for health promotion

Soyabean Oil is one of the few common vegetable oils that contain significant amount of alpha linolenic acid. Soyabean oil does contain significantly greater amount of Omega-6 fatty acids. 100 grams of Soyabean oil contains 7 grams of Omega-3-fatty acids, to 51 grams of Omega – 6; a ratio of 1:7 (Shun, 1997).

Lignins scavenge free radicals, bind carcinogens, in colon (Adlercreutz et al, 2000). Soya fibre may bind bile salt, derived from cholesterol and excrete them (Singh 2002).

Soyabees contain a high level of phytic acid, which has many effects including, acting as an antioxidant and a chelating agent. The beneficial claims for phytate include reducing cancer, minimizing diabetes and reducing inflammation (Vucenik et al, 2003 and Sudheer et al,2004).

The phytoestrogens present in Soya produce an oestrogenic activity 1/500 – 1/1000of that of oestradiol. They compete with oestradiol for response binding the phytoestrogen receptor complex does not undergo normal activation. So it has only a weak effect on the hormone response element of DNA (Bender, 2002).

They have two hydroxyl groups that are in the same position relative to each other as the hydroxyl groups in oestradiol, so that they bind to oestradiol receptors. They are naturally occurring substances in food that have a hormone like action. In the gut, bacteria convert isoflavones into substances that have an oestrogenic action, although they are not themselves hormones ( Glenville and Esson, 2004).

Soyabeans contains the isoflavones, genistein and daidzein (phytooestrogens), which reduces the risk of CHD and is useful in the prevention of cancer. Genistein also prevents plaque formation by preventing oxidation of LDL (Sacks et al,2006). Soya’s content of isoflavones are as much as 3mg/g dry weight. They exhibit similar structure to the mammalian steroid hormone 17 β estradiol (Watson, 2006).
Consumption of Soya protein instead of animal protein has been found to reduce serum concentrations of total cholesterol, LDL and triglyceride (Arliss and Biermann, 2002). One theory proposes that cholesterol absorption is impaired (or) altered (Dudek, 2001). Another theory postulates that phytooestrogens (isoflavones) bind to oestrogen receptors lowers LDL and increases HDL, cause vasomotor changes and arterial wall function (Dudek, 2001). Individuals need to consume about 25 grams of Soya protein (or) more each day to obtain cholesterol reduction (Wardlaw 2000).

FDA approved Soya as an official cholesterol lowering food along with other heart and health benefits. Soya phytoestrogens adsorbed on to the Soya protein were suggested as the agent reducing serum cholesterol levels. Isoflavones block the formation of blood clots and increases the flexibility of atherosclerotic arteries (Singh, 2002). Non-digestible compounds (phytosterols) blocks the cholesterol absorption from intestine and decrease LDL cholesterol levels. Soya protein increases the faecal excretion of bile acids. This in turn leads to increased LDL –C receptor activity and reduces blood cholesterol (VLDL and LDL) levels (Sacks et al, 2006).

Oestrogens may decrease lipoprotein(a) levels by upto 35% and it is postulated that the isoflavones found in Soya products may have a similar effect (Clarkson et al, 2011). They are natural phytoestrogens (Goyal 2009).

Protease inhibitor present in Soya inhibits cancer causing enzyme protease (Kennedy, 1995). Soya saponins boost the immune system and fight cancer (Plewa, 1999). A recently published meta-analysis of several epidemiological studies shows that the consumption of Soya foods decreases the risk of developing breast cancer in both pre- and post-menopausal women (Shu et al, 2009). Genistein, one of the phytochemicals found in Soya, can reduce the risk of cancer (Wardlaw, 2000). Genistein blocks cancer development by preventing tumors from creating blood vessels that would provide nourishment for growth (Arliss & Biermann, 2002).

Phytooestrogens are currently being researched to determine their usefulness in acting like synthetic oestrogen to protect women from bone loss and maintain a healthy heart (Wardlaw, 2000). Research suggests improvements
in bone mass in post-menopausal women and slowing of bone loss at the lumbar spine in perimenopausal women in response to feeding Soya protein with higher levels of isoflavones. Soya protein has been found to positively influence bone and calcium balance in post menopausal women (Arjimandi et al, 1998).

Studies show that “hot flashes modestly reduced in menopausal women consuming Soya protein with higher levels of isoflavones (Sacks et al, 2006). Increases in T4, free T3 and TSH have been reported in animals after feeding Soya protein in humans (Messina and Redmond, 2006). A component of Soya, isoflavone have a role in the development of atherosclerotic changes in the endothelium by decreasing cellular migration and proliferation (Sacks et al, 2006).

In recent studies, Soya protein contributed to the control of hyperglycaemia and reduced body weight hyperlipidemia, and hyperinsulinemia (Bathena & Velasquez, 2002).

2.12.4 Processing of Soyabean

During the processing of Soyabeans, they are first cleaned, then conditioned, cracked, dehulled and rolled into flakes. The next step is to remove the Soya oil from the flakes. The flakes are then dried, creating the “defatted Soyabean flakes”. This defatted material is the basis for the three major Soya protein products, flours, concentrates and isolates (Shun, 1997).

Soya Protein Products

Isolates

Soya protein isolate is a highly refined or purified form of Soya protein with a minimum protein content of 90% on a moisture free basis. It is made from defatted- Soya flour which has most of the non-protein components, fats and carbohydrate removed.

Soya isolates are mainly used to improve the texture of meat products, but are also used to increase protein content, enhance moisture retention, and acts as an emulsifier. Pure Soya protein isolate is used mainly by the food industry. It is usually found combined with other food ingredients (Shun, 1997).
Concentrates

Soya protein concentrate is about 70% Soya protein and is basically defatted Soya flour without the water soluble carbohydrates. It is made by removing part of the carbohydrates (soluble sugar) from dehulled and defatted Soyabeans. Soya protein concentrates are available in different forms; granules, flour and spray-dried (Shun, 1997).

Flours

Soya flour is made by grinding Soyabeans into a fine powder. It comes in three forms natural or full fat (contains natural oils) defatted (oils removed) with 50% protein content and with either high water solubility or low water solubility and lecithinated (lecithin added). Soya grits are similar to Soya flour except that the Soyabeans have been toasted and cracked into coarse pieces (Miniello et al, 2003)

2.12.5 Textured or texturized vegetable protein (TVP)

It is also known as textured Soya protein (TSP) or Soya meat. Soya meat is a meat analogue, or meat substitute made from defatted Soya flour, a by-product of making Soyabean oil. It is quick to cook, high in protein, and low in fat (Riaz, 2006).

TVP is made through a process known as “extrusion cooking”. A dough is formed from high PDI (protein dispersibility index) defatted Soya flour and water in a “preconditioner” (mixing cylinder) and cooled during passage through the barrel of screw type extruder such as Insta-Pro (or) Wenger model. Sometimes steam from an external source is employed to aid in the cooking process (Clark et al, 1991).

Upon exiting the die, superheated steam escapes rapidly producing an expanded spongy yet fibrous lamination of thermoplastic Soya flour which takes on the various shapes of the die as it is sliced into granules, flakes, chunks, goulash, steakettes, etc., by revolving knives and then dried in an oven (Clark et al, 1991).

Textured vegetable protein comes as granules, small dry chunks or flakes when bought in bulk. It has a little flavor of its own and needs to be
rehydrated and flavored (both can be accomplished in the same step), then added to cooking (Endres 2001).

TVP made from Soya flour contains 50% Soya protein and needs to be rehydrated before use at a weight ratio of 1:2 with water. However TVP when made from any concentrate contains 70% protein and can be rehydrated at a ratio of 1:3. It can be used as a meat replacement or supplement. The extrusion technology changes the structure of the Soya protein resulting in fibrous spongy matrix that is similar in texture to meat (Endres, 2001).

When stored dry, at room temperature TVP has a shelf of more than a year, but after rehydration it should be used at once or stored for not more than three days in the refrigerator. Rehydrated TVP is high in protein and low in fat and sodium. It is also a good source of fibre (Henk, 2005).

Textured vegetable protein (rehydrated) contains 14.3 g of Soya protein/100g TVP is an excellent source of Soya protein and isoflavone (Shun, 1997). TVP is usually made from a combination of Soya flour and Soya protein concentrate. Soya flour contains 50% protein and contain 5% fibre. Soya concentrate contains 65% to 70% protein and contains a small amount of fibre. Several components associated with Soya protein include trypsin inhibitors, phytates, saponins, isoflavones and fibres (Henk, 2005).

**Estimated Soya protein in Soya foods**

<table>
<thead>
<tr>
<th>Food</th>
<th>Soya protein (g.100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofu</td>
<td>10</td>
</tr>
<tr>
<td>Dried Soya beans</td>
<td>13.5</td>
</tr>
<tr>
<td>Tempeh</td>
<td>15</td>
</tr>
<tr>
<td>Soya grits</td>
<td>41</td>
</tr>
<tr>
<td>Soya compound</td>
<td>27.6</td>
</tr>
<tr>
<td>Soya flour (reduced fat)</td>
<td>46.5</td>
</tr>
<tr>
<td>Soya flour (full fat)</td>
<td>34.5</td>
</tr>
<tr>
<td>Soya milk (reduced fat)</td>
<td>3.6</td>
</tr>
<tr>
<td>Textured vegetable protein (rehydrated)</td>
<td>14.3</td>
</tr>
<tr>
<td>Soya breakfast drink</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Shun (1997)
4.12.6 Nutrient composition of Soya protein

Soya protein is considered a complete protein as it contains most of the essential amino acids that are found in animal proteins. The nutritional value of Soya protein is roughly equivalent to that of animal protein of high biological value (Young, 1991). For example, isolated Soya protein has a protein digestibility-corrected amino acid score 1.0 which is the same as that of casein and egg protein (Young, 1991). Soyabees provide one of the most abundant plant source of dietary protein. The protein content of Soyabean varies from 36% to 56% (Grishop et al 2001). The predominant proteins in Soya bean are the storage proteins, namely 7S globulin (conglycinin) and 11S globulin (glycinin) which comprise approximately 80% of the total proteins (Garcia et al, 1997). In addition, Soyabean also contains lecithin and protease inhibitors (Haytowitz et al, 1986). Soya protein is associated with fatty acids, saponin, isoflavones and phospholipids. Soya protein isolate (SPI) contains mainly lysophosphatidylcholines and lysophosphatidylethanolamines (Fang et al 2004). Soya proteins contain low Methionine/glycine and lysine/arginine ratios compared to casein (Gudbrandsen, et al, 2004).

Soyasaponins are one of the major classes of phytochemicals present in Soya (Berhow et al, 2006). Saponin content in different varieties of Soyabees range from 13-42 umol/g in the Germ and from 3-6 umol/g in the cotyledon (Hubert et al, 2005).

Soya protein is unique among the plant-based proteins in that it is the only plant protein that contains largest concentrations of isoflavones. The amount of isoflavones in Soyabees varies depending upon the type of Soyabean, geographic area of cultivation and harvest years of Soyabees (Caldwell et al 2005). In addition, isoflavone contents in different Soya products also vary substantially due to differences in methods of processing (Wang and Murphy 1994). Soyabees and commercially available Soya products like Soya flour and textured Soya protein provide the highest concentrations of isoflavones, 0.1-5mg total isoflavones/g Soya protein (USDA , 2002).
2.12.7 Mechanisms of actions of Soya protein

Several lines of evidence suggest that Soya protein may favourably affect lipid absorption, insulin resistance, fatty acid metabolism and other hormonal, cellular, or molecular changes associated with adiposity. Studies in animals indicate that Soya protein ingestion exerts its lipid-lowering effect by reducing intestinal cholesterol absorption and increasing fecal bile acid excretion, thereby reducing hepatic cholesterol content and enhancing removal of LDL (Greaves et al 2000). Dietary Soya protein has also been shown to directly affect hepatic cholesterol metabolism and LDL receptor activity (Kirk et al, 1998).

Lovati and co-workers (1985) demonstrated an increased binding of VLDL to liver membranes of hypercholesterolemic rats fed on a diet containing Soya protein, suggesting altered hepatic metabolism with increased LDL and beta-VLDL removal by hepatocytes. In another study he (Lovati et al, 1987) had also shown that Soya protein diet consistently increased degradation of LDL, even in the presence of an elevated cholesterol intake. Dietary Soya protein reduces insulin/glucagon ratio, which may contribute to the hypocholesterolemic effect of Soya protein. Gudbrandsen et al (2006), has shown that feeding obese rats with Soya protein concentrate enriched with isoflavones for 6 weeks reduced fatty liver and decreased the plasma levels of alanine transaminase and aspartate transaminase. These effects were accompanied by increased activities of mitochondrial and peroxisomal beta-oxidation, acetyl-Co carboxylase, fatty acid synthase and glycerol-3-phosphate acyltransferase in liver increased plasma triacylglycerol level, and decreased hepatic mRNA level of VLDL receptor.

Soya protein reduces liver triglycerides or fat by partly inhibiting hepatic fatty acid synthesis in the liver. ACC (acetyl-CoA carboxylase), the rate-limiting enzyme that catalyses the carboxylation of acetyl-Co A to form malonyl-CoA, is the pivotal enzyme in the biosynthesis of long chain fatty acids (Dick, et al 2000). Recently dietary SPI has also been shown to reduce the expression of ACCa and ACCb isoforms mRNA and protein contents in the liver of rats (Xiao, et al., 2006). A similar reduction of hepatic ACCa mRNA-expression by Soya protein was also found in another study by Aoki et al (2006), in which rats were fed SPI diet.
Mezei et al (2003), showed that consumption of high-isoflavone Soya protein diet improves glucose tolerance, insulin resistance, and hepatic cholesterol and triglyceride concentrations in obese rats. Soya protein improves insulin resistance and lipid levels by activating peroxisome-proliferator activated receptors (PPARs), which are nuclear transcription factors that regulate the expression of genes involved in glucose homeostasis, lipid metabolism, and fatty acids oxidation ((Morifuji, 2006).

Morifuji et al (2006), also demonstrated that Soya protein feeding in rats decreased hepatic triacylglycerol levels and epididymal adipose tissues weight. These changes were associated with increased activity and mRNA levels of several skeletal muscle enzymes involved in fatty acid oxidation, including carnitine palmitoyltransferase (CPT1) activity beta-hydroxyacyl-CoA dehydrogenase (HAD), acyl-CoA oxidase, and medium chain acyl-CoA dehydrogenase.

Soya protein may reduce adiposity by modulating the expression of sterol regulatory element binding proteins (SREBPs), a family of transcription factors that controls multiple genes involved in fatty acid and cholesterol synthesis. In obese rats, Soya protein feeding was shown to reduce the expression of the hepatic SREBP-1 (the principal regulator of hepatic fatty acid biosynthesis) and its target genes fatty acid synthase (FAS), steryl-CoA-desaturase-1 and delta-5 and delta-6 desaturases (Tovar, et al, 2005).

Soya protein intake may limit adiposity by reducing the number of dysfunctional adipocytes possibly as a result of low lipogenesis. Soya protein may also reduce hepatic lipotoxicity by maintaining the number of functional adipocytes, preventing the transfer of fatty acids to extra adipose tissues (Tovar et al,2005).

Another possible mechanism of action of Soya protein is stimulation of adiponectin, a cytokine produced by fat cells that plays a key role in regulating adipocyte differentiation and secretory function, and in enhancing insulin sensitivity (Lihn et al, Fu et al, 2005). Plasma levels of this hormone are reduced in obesity (Arita et al 1999,Wyur et al 2001). Dietary SPI(Soya protein intake) intake is associated with increased plasma concentration of adiponectin in rats, suggesting that Soya protein may modulate adiponectin production (Nagasawa, 2002).
Certain polypeptides or subunits of Soya protein have been shown to mimic some of the effects of dietary Soya protein on food intake and lipid metabolism. In a rat study, oral administration of the Soyabean-beta-conglycinin peptone, suppresses food intake and gastric emptying (Nishi et al, 2003). These effects were attributed in part to an increase in circulating levels of cholecystokinin.

A Soyabean beta-conglycinin diet was also shown to lower serum triglyceride, glucose and insulin levels in normal and genetically obese mice. These effects were accompanied by reduced hepatic fatty acid synthase activity and increased activities of two enzymes, related to fatty acid beta-oxidation and mRNA of acyl-CoA oxidase levels, as well as increased fecal excretion of triglycerides, indicating that Soya beta-conglycinin reduces serum TG levels by suppression of hepatic acid synthesis, acceleration of beta-oxidation, and/or increased TG fecal excretion (Moriyama et al, 2004).

In a study of golden Syrian hamsters, a diet containing group Beta Soya saponins, (with no isoflavones) was shown to lower plasma total cholesterol, non-HDL cholesterol, triglycerides, and the ratio of total cholesterol to HDL-cholesterol (Lee et al, 2004). These changes were associated with increased fecal excretion of bile acids and neutral sterols.

A greater reduction of serum cholesterol as well as total lipid and cholesterol concentrations in liver was also observed when rats were fed a Soya protein hydrolysate with bound phospholipids, compared to Soya protein diet alone or Soya protein-hydrolysate (Nagaoka et al, 1999).

Soya isoflavones have been shown to decrease fat accumulation in certain depots in some animal models of obesity (Ali et al, Banz et al, 2004). Manzoni et al (2005), has shown that consumption of a high isoflavone-containing Soya diet improved glucose tolerance and reduced liver triglyceride and cholesterol concentrations in obese rats. Exposure to Soya isoflavone also increased HMG CoA reductase protein levels and HMG CoA synthase mRNA levels and increased both HMG CoA synthase and LDL receptor promoter activity, indicating that isoflavones may also regulate the genes involved in cholesterol biosynthesis and homeostasis (Mullen et al, 2004).

Thus, certain polypeptides (such as 7S globulin or conglycinin), Soya saponins, phospholipids, and isoflavones (genistein and daidzein) present in Soyabean appear to have complimentary actions on fatty acid and cholesterol
metabolism, which may contribute to the overall beneficial effects of Soya protein, in obesity and associated lipid abnormalities.

### 2.12.8 Soya protein and Obesity

An increasing body of literature suggests that Soya protein and its isoflavones may have beneficial role in obesity. Several nutritional intervention studies in animals and humans indicate that consumption of Soya protein reduces body weight and fat mass in addition to lowering plasma cholesterol and triglycerides. In animal models of obesity, Soya protein ingestion limits or reduces body fat accumulation and improves insulin resistance, the hallmark of human obesity (McAuley et al, 2006).

Animal studies have shown that Soya protein suppresses appetite, in part, by stimulating the release of cholecystokinin(CCK), which regulates satiety, and gastric emptying (Nishi, 2003). Feeding Soya protein is also associated with lower body weight and lower body fat in rats and mice (Nagasawa, 2002).

High quality protein, such as that provided by Soya, help to preserve fat free mass (FFM) during weight loss. In obese humans, dietary Soya protein also reduces bodyweight and body fat mass in addition to reducing plasma lipid, including decrease in triglycerides, insulin levels and increase in LDL particle size (Westerterp, 2007).

Jenkins et al (2009) evaluated the effects of a high vegetable protein diet, “Eco-Atkins diet” that included Soya protein, compared to a high carbohydrate, lacto-ovo vegetarian diet in overweight, hyperlipidemic men and women, and found that in addition to weight loss benefits, those who consumed the high vegetable protein diet experienced significantly greater reductions in LDL cholesterol, total cholesterol: HDL cholesterol ratios (TC/HDL ratio) and apolipoprotein B: apolipoprotein A-I ratios. Another recent study of men and women with type 2 diabetes, compared the effects of milk protein isolate to Soya protein isolate and found that serum LDL-cholesterol, LDL cholesterol:HDL cholesterol ratios and apolipoprotein B: apolipoprotein A-I ratios were reduced significantly more with Soya protein (Pipe et al, 2009).
Hurley et al (1998), examined the metabolic effects of varying dietary protein and carbohydrate source in rats. These investigators fed male rats for 28 days with semi-purified diets that varied in both protein and carbohydrate sources, namely Soya protein isolate (SPI)-cornstarch, SPI-sucrose, cod protein(COD)-cornstarch, COD-sucrose, casein-(CAS)-cornstarch, CAS-sucrose. Rats fed with SPI-cornstarch showed lower total body energy and fat gains compared to animals fed with other diet combinations of either CAS-cornstarch, CAS-sucrose. Plasma glucose and insulin concentrations were also significantly lower in SPI-cornstarch diet than in those fed with the CAS-sucrose diet. The reducing effect of SPI-cornstarch diet on body fat gain may be related to reductions in energy intake and due to plasma glucose concentrations.

Davis et al, (2005), evaluated effects of casein and Soya protein on body weight, plasma total cholesterol, and insulin sensitivity in male lean SHHF (+/cp) rats, an unique rodent model that exhibits the early features resembling the metabolic syndrome in humans. Rats fed with Soya protein (with either low or high isoflavone content) for 36 weeks had significantly lower body weight, total plasma cholesterol, fasting blood glucose and plasma insulin compared to rats fed on casein.

Iritani and co-workers (1996) studied the effects of dietary Soya protein on body weight, plasma and liver triacylglycerol concentrations and lipogenic enzyme gene expression in livers of genetically obese rats. Obese rats and their lean littermates were fed casein or Soya protein isolate diet containing fat (4% hydrogenated fat plus 1% corn oil) or corn oil (5 %) for 3 weeks. After 3 weeks feeding, the fatty rats fed Soya protein had lower body weight than those fed with casein. Moreover, the hepatic messenger RNA concentrations and activities of lipogenic enzymes were found to be lower in rats fed with Soya protein, than in, those fed on casein, regardless, of genotype or dietary fat. Thus, dietary Soya protein appears to have anti-obesity effect but only when a diet low in polyunsaturated fatty acids is consumed.
In another study, Aoyoma et al (2000), compared the effects of an energy-restricted, low-fat and high protein (35%) diet with either Soya protein isolate (SPI) and its hydrolysate (SPI+H) or casein in male rats made obese by feeding high fat diets containing 30% fat and in genetically obese yellow mice. They showed that body fat content and plasma glucose levels were significantly lower in mice fed on SPI and SPI+H diets than those fed with casein. In rats, plasma total cholesterol level was lower with the SPI+H diet than with the casein diet.

In a longevity study of obese and lean rats, Johnson et al (1997), showed that feeding them a Soya protein diet ad libitum from 4 weeks of age remarkably prolonged their survival. Moreover, pair-feeding obese rats with lean control rats prevented hyperphagia (with 8-18% restriction in energy intake) and also increased maximum life span.

Bosello et al (1998), evaluated the short and long term effects of hypocaloric diets containing proteins from two different sources on body weight and plasma lipids in obese subjects. In this study, 24 obese patients, aged 25-42 years of at least 50% above ideal weight, were divided into two groups; one group received casein and the other group, Soya protein. Both diets were hypocaloric and contained the same amount of protein. The subjects initially received 375kcal/day for the first 15 days, followed by 425 kcal/day for the succeeding 60 days. All subjects lost weight but the reduction in body weight was similar in both groups after the two periods of caloric restriction, but the percent changes were greater in the Soya protein group than in the casein group. Plasma triglyceride was reduced in subjects who received Soya protein but not in the group that received casein. These results show that substitution of Soya protein can be of benefit in obese patients who need a long term hypocaloric diet.

Yamashita et al (1998), compared the effects of meat based diet with a plant based diet in 36 overweight or obese women, age 40± 9 years. Both diets were designed to provide similar energy intake but one contained red meat and the other Soyabean as the major protein source. After 16 weeks on the diet, subjects in both diet groups lost weight ((9% of body weight) and showed similar decreases in plasma total cholesterol, LDL Cholesterol, triacylglycerol and leptin levels. There was a significant reduction in the waist to hip ratio in both
groups of subjects, suggesting that the weight loss induced by both diets was due in part to a decrease in abdominal fat.

Mikkelson and coworkers (2000), compared the effects of fat-reduced diets containing either pork-meat protein, Soya protein and carbohydrate on 24-h energy expenditure in 12 young overweight and mildly obese men (body mass index=26-32). Diets were isoenergetic pork diet (29% of energy as fat and 29% as protein) Soya diet (29% of energy as fat and 28% as protein); and carbohydrate diet (28% of energy as fat and 11% as protein) and were administered for 4 days. After 4 days of each dietary intervention, 24h-energy expenditure measured in a respiratory chamber was significantly higher with the pork or Soya diet than with the carbohydrate diet.

Nagasawa et al (2002), evaluated the effect of a calorie-restricted diet containing Soya protein isolate (SPI) on body fat components, plasma glucose lipid and adiponectin levels and expression of genes involved in glucose and fatty acid metabolism in obese male mice. Body weights and adipose tissue weights of mesenteric, epididymal and brown fat were lower in mice fed on SPI diet. Plasma cholesterol, triglyceride, FFA (free fatty acids) and glucose levels were also decreased by the SPI diet. Body fat content and plasma glucose levels in mice on a SPI diet were still lower than those treated with an isocaloric casein protein diet.

Allison et al (2003), performed a 12 week study on a low calorie Soya-based meal replacement programme in 100 obese subjects. Subjects were randomized to either the meal replacement treatment group (240g/day, 1200 kcal/day) or control group for a duration of 12 weeks. Subjects treated with Soya-based meal replacement formula lost more weight (7.0 vs 2.9Kg) and significantly greater reductions in body fat mass, total cholesterol and LDL cholesterol than the control subjects.

Deibert et al (2004), compared the effects of three different interventions containing lifestyle education (LE-G) or a substitutional diet containing high-Soya protein, low-fat diet with (SD/PA-G) or without (SD-G) guided physical activity program in 90 pre-obese and obese subjects with a mean body mass index (BMI) of 31.5. Subjects were randomly assigned to one of the three interventions for 6 months. All 3 interventions significantly reduced BMI by about 2-3 kg/m2.
However, subjects treated with SD-G and SD/PA-G lost more weight and had a greater decrease in body fat mass than those treated with LE-G. By contrast, no significant differences were observed in lean body mass between the three treatment groups. This study indicated that a high Soya-protein and low fat diet can improve body composition and produce greater loss in body weight and fat mass without losing muscle mass in overweight and obese individuals.

Anderson and Hoie (2005), compared the effects of Soya-versus milk-based replacements (MR) in overweight and obese women (BMI of 27-40 kg/m²) who consumed low energy diets (LED), for a period of 12 weeks. Subjects were randomly assigned to LED provided 1200kcal/day with consumption of five Soya-based or two milk-based liquid MR for 12 weeks. Subjects who consumed Soya-MR had greater weight loss than who consumed milk-MR (9.0% to 7.9%). There were significantly greater reductions in total cholesterol, LDL cholesterol and triglyceride levels with Soya-MR than with milk-MR (Meal replacement formula).

4.12.9 Soya in Heart Health

Coronary heart disease (CHD) is the major cause of death in most developed countries and is rapidly increasing in prevalence in developing countries (Rosamond et al, 2008). While many risk factors, such as cigarette smoking and hypertension, contribute to risk for CHD, lipid abnormalities are the major factors. Low-density lipoproteins (LDL) have a central role, in the atherosclerotic process. LDL penetrate the walls of blood vessels where they are oxidized by free radicals and accumulate as a gruel-like material that blocks the blood vessel lumen; this material also can leak into the blood vessel to cause thrombosis. High-density lipoprotein (HDL) cholesterol has a protective effect and act to prevent LDL oxidation and remove cholesterol that accumulates in the blood vessel wall (Anderson, 1997).

Soya protein exerts several anti-atherogenic effects. First it decreases LDL cholesterol levels significantly. Second, it tends to increase HDL – cholesterol levels; this is rather unique since most dietary interventions such as oat bran intake or decreased saturated fat intake significantly decrease HDL-cholesterol levels. Third, Soya isoflavones, plant chemicals unique to Soyabeanes, have antioxidant properties which protect LDL from oxidation,
Fourth, Soya isoflavones have favourable effects on blood vessel function (Anderson, 1997).

Diet has a major impact on several modifiable risk factors for heart disease; hypercholesterolemia, hypertriglyceridemia, elevated LDL cholesterol, low LDL cholesterol, hypertension, obesity and diabetes. There is increasing evidence that consumption of Soya protein in place of animal protein lowers blood cholesterol levels and may provide other cardiovascular benefits (Anderson, 1997). Epidemiologists have long noted that Asian populations who consume Soya foods as a dietary staple have a lower incidence of CVD than those who consume a typical Western diet (AHA, 1999).

**Mechanism of action**

Animal studies indicated that certain amino acids, especially lysine, increase blood cholesterol levels, while arginine counteracts this effect. Soya protein provides a more favourable arginine to lysine ratio than casein. The two globulins, 11S and 7S, which are the major storage proteins in Soyabeans may be involved in direct up-regulation of liver or peripheral lipoprotein receptors (thus removing them from circulation) (Kurowska et al, 1994).

Soya fibre has a hypocholesterolemic effect when added to other foods (Wang et al, 1994). Soya rich diets provide phytic acid. A theory propounded is that phytic acid may lower cholesterol levels by chelating zinc and allowing more copper to be absorbed, consequently decreasing the ratio of zinc to copper (Zhou et al, 1995). Saponins may contribute to cholesterol lowering by increasing bile excretion (Shorey et al, 1985).

Heat-stable Bowman Birk inhibitor may increase the secretion of cholecystokinin, which in turn stimulates the gallbladder and increases secretion of bile into the gastrointestinal tract.

Isoflavones exert an oestrogenic effect and bind to two types of oestrogen receptors (ER alpha and ER beta). Isoflavones found in Soya include genistein, daidzein and glycetein. Genistein binds rather weakly to ER alpha (about 1/20 the affinity of 17-betaestradiol) but with much higher affinity to ER beta (about 1/3, the affinity of 17 beta estradiol). Oestrogen has been shown to decrease LDL cholesterol and increase HDL cholesterol. They have a role in
the up-regulation of depressed LDL receptors in the liver cells. This results in increased LDL uptake by the liver and lowering of serum LDL and hence lowering of serum cholesterol levels (Kuiper et al, 1997).

Crouse et al (1999), reported that the cholesterol-lowering effect of Soya protein is entirely due to isoflavones. Genistein is known to inhibit tyrosine kinase, an enzyme involved in the cascade of events leading to formation of thrombi lesions. Isoflavones also act as an antioxidant and can inhibit LDL oxidation.

Isoflavone extract from Soya improved systemic arterial elasticity in women without effects on blood lipid levels. In fact, animal suggests that Soya oestrogens (i.e.isoflavones) may account for 60-70% of hypocholeserolemic effect of Soya protein. There is an interruption in intestinal absorption of bile acids and dietary cholesterol when Soya protein is consumed. This causes cholesterol to be removed from the body, resulting in increased liver synthesis of cholesterol for enhanced synthesis of bile acids and in greater LDL-cholesterol receptor activity. The liver responds by increasing the number of LDL receptors, causing fall in blood cholesterol (Nestel, 1997).

It is widely accepted that oestrogens reduce risk for CHD. Oestrogen decreases LDL-cholesterol, increases HDL-cholesterol and improves vasomotor tone and vessel wall compliance. Soya isoflavone may act as an oestrogen like compound and produce effects similar to that of oestrogens. The higher arginine to lysine ratio of Soya protein may decrease insulin secretion and increase glucagon secretion, which would then inhibit lipogenesis (Potter, 1995). In animal studies, thyroxine levels increased with consumption of Soya protein (Forsythe, 1995 and Balmir et al, 1993). High thyroxine levels were theorized to decrease cholesterol levels, but human studies have been inconsistent (Ham et al, 1993 and Sirtori et al, 1995).

An increase in LDL receptors result in increased LDL cholesterol removal from blood. On the basis of several clinical studies, Sirtori et al (1995), concluded that Soya protein up-regulates depressed LDL receptors in humans.
Studies show that genistein, and to a lesser extent, other isoflavones found in Soya products have potential antioxidant activity, hence prevents CVD (Kanazawa et al, 1995 and Kapiotis et al, 1997). Shige et al (1998), concluded that consuming 20g/day of isolated Soya protein favorably affects post prandial remnant lipoprotein response.

One of the essential steps in the atherosclerotic process is the adherence of platelets to form foam cells and the subsequent increase in growth factors released from platelets. In vitro studies (Raines et al, 1995 and Wilcox,1995), on genistein has been shown to:

a) Interfere with the activation and accumulation of platelets;

b) Reduce the production of platelet-derived growth factors, which are believed to play an important part in the proliferation of smooth muscle cells in atherosclerotic plaque

c) Inhibit the action of thrombin, an enzyme that converts fibrinogen into fibrin to form a blood clot.

High isoflavone intake was associated with reduced risk of cerebral infarction and myocardial infarction in Japanese women. The risk reduction was pronounced for postmenopausal women (Kokubo et al, 2007)

In a study by Honore et al (1997), showed that constricted arteries in female monkeys were dilated on feeding isoflavones intact Soya on administration of genistein. In a study on monkeys, Anthony et al (1997), found that Soya + (Soya with isoflavones) group had the least coronary artery atherosclerosis lesions 90% less than in the casein group and 50% less than in the Soya – group (Soya without isoflavones). Wagner et al (1997), proposed that protein may also act at the level of the artery wall to reduce LDL accumulation in a male monkey.

In a meta-analysis of 38 controlled clinical studies concluded that substituting Soya protein for animal protein significantly lowered total cholesterol, LDL cholesterol and triglycerides without affecting HDL cholesterol. These effects were greater in subjects with higher baseline cholesterol values. Daily Soya protein consumption, on an average 47g/day resulted in a 9.3% decrease in total serum cholesterol, a 12.9% decrease in LDL
cholesterol and a 10.5% decrease in triglycerides. Studies included in the meta-analysis used Soya protein in the form of either TVP or ISP. No difference in efficacy was noted between these sources of Soya protein, although the composition of these Soya products were quite different (Anderson et al, 1995).

**Studies in Adults with Normal Cholesterol Levels**

Consumption of Soya protein does not appear to have a hypocholesterolemic effect in adults with low or normal cholesterol levels. In a study of 12 adults with a mean total cholesterol level of 145 mg/dl at baseline, the incorporation of 66 to 80 g Soya (meat replaced by Soya analogues and milk replaced by Soya beverage) resulted in no significant changes in serum lipids (Giovannetti, 1986). Wong et al (1998), found no significant change in normocholesterolemic men 20 to 50 years of age (mean baseline total cholesterol, 169mg/dl) who consumed 50g Soya protein in addition to a diet low in saturated fat and cholesterol.

In the meta-analysis of the effect of Soya protein on serum cholesterol levels subjects with normal cholesterol levels, who had initial values below 200 mg per deciliter, had non-significant reductions of 3.3 per cent while receiving the Soya protein diet. Those with mild hypercholesterolemia, who had initial values of 200 to 255mg per deciliter (5.2 to 6.6 mmol per liter) had significant reductions of 4.4 per cent. Subjects with hypercholesterolemia, who had initial values of 250 to 333mg per deciliter (6.70 to 8.61mmol per liter) had significant decreases of 7.4 per cent. Subjects with severe hypercholesterolemia, whose initial values were above 335 mg per deciliter (8.66mmol per liter), had significant reductions of 19.6 per cent. Changes in serum HDL cholesterol concentrations were similar for all quartile (Anderson et al, 1995).

**Studies in Adults with Elevated Cholesterol Levels**

In a study, post-menopausal women on a diet low in saturated fat and cholesterol (NCEP Step I diet) consumed 40g/d of Soya protein with either 56 or 90 mg of isoflavones daily or casein for 6 months. Both Soya groups had significantly better blood lipid profiles (average change from baseline, 8.2%
A decrease in non-HDL cholesterol and 4.4% increase in HDL cholesterol) than the casein group. However, no differences in lipids were seen between the 2 isoflavone levels (Baum et al, 1998). HDL significantly increased from baseline with consumption of 32 g Soya protein as Soyamilk in both women and men with hypercholesterolemia (Kurowska et al, 1997).

A 9 week study comparing the effects of Soya protein (25g/d) containing varying levels of isoflavones with those of casein found that consumption of the highest isoflavone level (62mg/d) resulted in significantly lower total (6%) and LDL (4%) cholesterol values than those of the casein group (Crouse et al, 1999).

A dose-response study in hypercholesterolemic men on an NCEP Step I diet used 20,30,40, or 50g/d of Soya protein compared with casein. After 6 weeks, all levels of Soya consumption led to significantly greater reductions in non-HDL cholesterol (1.5% to 4.5%) than did the casein, with higher levels being more effective (Teixeira et al, 2000). Bakhit et al (1994), showed cholesterol lowering with as little as 25g/d of ISP in hypercholesterolemic but not normocholesterolemic men.

The FDA recently published its final ruling on a food-labelling health claim for Soya protein and cholesterol reduction stating that 25g/d of Soya protein, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease (FDA, 1999). Thus Soya protein makes diet therapy a much more potent tool than a low fat diet alone.

Similar to Soya, invention of indigenously prepared dietary supplements for weight loss through traditional Indian system of medicine are considered to be a suitable alternative. Several botanicals including Gymnema sylvestre, Garcinia cambogia, Piper longum and Zingiber officinale have been found to have therapeutic benefit for the treatment of obesity. Caralluma fimbriata, an edible cactus have been reported to have similar anti-obese effects.

2.13 CARALLUMA AND OBESITY

In keeping with the holistic approach, native populations of India, consume several locally growing medicinal plants including cactus as part of their diet.

The Caralluma genus is one such genus of cacti, which has several species, many of which grow across India. It has about 100 species distributed in the driest
parts of India, Arabia, Pakistan, Africa and Myanmar. Out of 14 species reported from India, 11 species are concentrated over Peninsular India, 5 species and 5 varieties are strictly endemic to India. A number of Caralluma species are being used by local inhabitants for their primary health care. Plants of this genus are used as food and appetite suppressor among the poor people (Pullaiah et al 2008).

Caralluma fimbriata, is the most prevalent of these species and it flourishes in large parts of interior India. It is an edible, succulent cactus grown wild all over India and is part of the daily diets of several native populations. It grows wild in urban centers as well and is planted as a roadside shrub and as a boundary maker in gardens (Preuss, 2007).

Caralluma fimbriata is essentially a vegetable of daily use in tribal India. It is eaten in several forms It is cooked as a regular vegetable, with spices and salt. It is used in preserves like chutneys and pickles and it is even eaten raw (Preuss, 2007)

### 2.13.1 Botanical descriptions

| Caralluma fimbriata (Roxbury) Family | Asclepiadaceae |
| Synonym | Caralluma ascendens |
| Local names | Kullee Mooliyan, Kallimudayan (Tamil) |
| | Karallamu (Telugu) |
| | Yugmaphallottoma (Sanskrit) |
| | Ranshabar Makadsenguli, shindala makadi (Marathi) |

This large group consists of tender succulents, found wild in Africa, the Canary Islands, India, Arabia, Southern Europe, Ceylon and Afghanistan. The plants of this group vary from thin, recumbent stems from ½ to 1½ inches thick to erect growing clumps, upto 8 inches high. The spines that cover the angled stems are actually leaves. The star-shaped, fleshy flowers of these plants are some of the worst smelling of the succulent plants. Ordinarily borne in late summer, the foul smelling blossoms are usually coloured black, purple, yellow, tan, maroon, red (or) dark brown. They vary from ½ to 2 inches and are borne at the base of the plant. In the wild, these blossoms are pollinated by flies, which are greatly attracted to the plant (Laddha, 2003).
Other species of Caralluma genus are Caralluma indica, Caralluma attenuata, Caralluma umbellata and Caralluma stalagmifera. All these varieties of Caralluma are botanically and phytochemically similar to Caralluma and regularly consumed by the native population across India (Wealth of India, 1992).

### 2.13.2 History of use

Caralluma fimbriata has been in use since centuries in India. It is commonly used as a vegetable in several regions of India. Indian tribals chew chunks of Caralluma fimbriata to suppress hunger when on a day’s hunt. The cactus is used among the labour class in South India to suppress appetite and enhance endurance. The Tribesmen states that, their energy levels are maintained without food and water and that they do not feel any fatigue (or) tiredness. Daily consumption of Caralluma fimbriata by the Tribesmen in this manner is estimated to be about 100 g. In the Kolli hills of South India, Caralluma fimbriata is a vegetable used daily. In the arid regions of Andhra Pradesh, Caralluma fimbriata is used in pickles and chutneys (Wealth of India, 1992).

In Western India, Caralluma fimbriata is well known as a fair famine food, appetite suppressant and thirst-quencher. The green follicles are eaten, boiled and salted. In Kerala, of South India, Caralluma fimbriata is used as a vegetable and appetite suppressant among tribal populations. It also finds use today as an appetite suppressant and famine food during times of famine in the semi-arid regions of India. (Radhakrishnan et al, 1999).

It has been used as an appetite suppressant in India since Vedic times and also been used in the medicine to treat various conditions such as diabetes, fever, pain and inflammation. In folklore medicine, plants of the Caralluma species have been used to treat diabetes (Radhakrishnan et al, 1999).

Medicinal properties of Caralluma species include carminative, febrifugal, antihelmintic, antirheumatic, antidiabetic and hypoglycaemic, antipyretic, anti-inflammatory, antinociceptive and antioxidant effects. It showed modest antibacterial activity against Klebsiella pneumonia, Escherichia Coli, Bacillus subtilis and Salmonella typhi. Hence it can be used as a wonder drug for respiratory tract infections (Nrupen and Samrat, 2008).

In vitro antioxidant activity and phenolic constituents of the methanolic extracts of Caralluma fimbriata was screened. The data obtained from the study showed that Caralluma had a high level of antioxidant activity and antioxidant
constituents like total phenols and flavonoids were present (Maheshu and Sasikumar, 2010).

### 2.13.3 Caralluma fimbriata – phytochemical constituents

The key phytochemical constituents are the pregnane glycosides (Hayashi et al, 1988 and Abdel et al, 2002), flavones glycosides, Megastigmane glycosides, bitter principles, saponins (Bader et al, 2003), various flavonoids (Kamil et al, 1999) etc. The specific active components present in Caralluma fimbriata are, Caratuberside A, Bouceroaside VII, Caratuberside B, Bouceroaside VIII, Bouceroaside I, Bouceroaside IX, Bouceroaside II, Bouceroaside X, Bouceroaside III, Tomentogenin, Bouceroaside IV, Sitosterol, Bouoeroside V, Luteolin 4 – neohesperidoside, Bouceroaside VI and Kaempferol – 7 – 0 – neohesperidoside (Leo et al, 2005).

The pregnane glycosides are common to the Caralluma genus and various congeners are to be found in all Caralluma species, including Carafluma fimbriata (Leo et al, 2005). Eleven pregnane glycosides from Caralluma fimbriata have been isolated (Yuliana et al, 2010).

#### Table 2.13.3

**Chemical Components of the pregnane glycosides**

X=gal[3-o-m,e,6-deoxy](4→1)glu.

<table>
<thead>
<tr>
<th>Pregnan glycosides</th>
<th>Molecular formula</th>
<th>Molecular weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caratuberside A</td>
<td>C34H57O12</td>
<td>675.819</td>
</tr>
<tr>
<td>Caratuberside B</td>
<td>C34H59O12</td>
<td>659.835</td>
</tr>
</tbody>
</table>

Pure Caratuberside A is a white crystalline substance. Melting point is 170-171°C. Rotation is $[\alpha]_D$ at 20°C $D+60'$ (C=0.66 in methanol)

Pure Caratuberside B is a white crystalline substance. Melting point is 182-188°C (Preuss, 2007).

Pregnan glycosides can be used for medicinal purposes and as food additives, such as in treatment of obesity, in reduction of blood glucose, in reduction of blood pressure, in reduction of hip, waist and arm circumference, in reduction of fat, increase of BMR, in the decrease of BMI, increase of lean body mass, as an appetite suppressor, and in the reduction / (or) elimination of joint pains and in the enhancement of energy levels (Preuss, 2007).
Pregnane glycosides of Caralluma exhibit a three-fold action on the fat metabolism in human subjects. The three actions are:

i) Reduction of fat synthesis by inhibiting the generation of acetyl-coenzyme A and malonyl-coenzyme A.

ii) By reducing malonyl-coenzyme A levels, the balance is swung in favour of the enzyme carnitine acyltransferase which enhances fat catabolism (lipolysis); and

iii) Interference in the action of malonyl-coenzyme A which is involved in fat synthesis

(Rajendran and Venkatesh, 2007).

Other benefits include, increase in lean body mass, enhancement in the ratio of blood HDL/LDL, improvement in capillary health, memory function, joint inflammation and others (Kunert et al, 2008).

### 2.13.4 Safety Considerations:

1. The cactus has been in the food chain of India for years and has not been associated with any significant adverse side effects; the average intake ranged about 100-400 grams of Caralluma plant extract.

2. Caralluma fimbriata is listed in the Wealth of India as a famine food.

3. Various testimonial by doctors and scientists confirm to its safety.

4. Testimonials by individuals who regularly consume the product describe its safety.

5. The daily dose of the extract contains the same concentrations of ingredients, as commonly eaten daily in the raw vegetables.

6. A study to determine LD 50 did not disclose toxicity, and it was reported that the LD 50 exceeded 5 g/kg.

7. The heavy metal content of Caralluma extracts was found to be quite low within limits based on several separate investigations.

8. Low amounts of hexane, methanol, 2-propanol, chloroform,1,4dioxane, methylene chloride and trichloroethylene were present in Caralluma extracts (Preuss, 2007).
Inspite of the long history of daily consumption of Caralluma fimbriata, in India, no adverse events have ever been reported and therefore it was thought appropriate to develop and clinically test a hydroalcoholic extract of Caralluma fimbriata.

Based on the traditional usage of the herb a standardized extract of Caralluma fimbriata developed by Gencor-Pacific Limited, in partnership with Green Chem, India, was designed and developed. A full-spectra aqueous alcoholic extract of the herb was developed to ensure that all of the vital constituents of the herb were present in the product. High-pressure liquid chromatography and other techniques were used to validate the profile of the raw herb, dried herb and final extract, to ensure and verify that consumption of 100 g of the herb by the tribal’s was equivalent to consumption of 1 g of the standardized extract. The extract was standardised for pregnane glycosides, saponin glycosides and bitter principles (Kuriyan et al, 2007).

About 12 kg of dried herb was obtained from 100 kg of the fresh plant, which gave a final yield of 1 kg of the extract. It was then purified, granulated and filled in capsules to deliver 500 mg of the extract (Kuriyan et al, 2007).

2.13.5 Toxicological evaluation of Caralluma fimbriata extract

The acute oral toxicity was determined in female and male, Wistar rats, after the oral administration of 2 g/kg body weight, for sighting study and 5 g/kg body weight for main study. All animals survived until the scheduled necroscopy at the end of the study period of 14 days. Therefore CFE did not produce signs of toxicity at very high doses of 5 g/kg and it showed that LD50 was more than 5 g/kg. Histology revealed no abnormalities in various organs (Venkatraman, 2004).

A mutagenicity study (reverse mutation test on Caralluma extract by salmonella typhimurium) was conducted by Intox Private Limited, India. The study was in accordance with OECD Principles of good laboratory practices (OECD,1998) and OECD guidelines for testing of chemicals(2001). The study concluded that Caralluma extracts are non-mutagenic in Salmonella typhimurium strains TA 1535, TA 87A,TA 100,TA 112 (Deshmukh and Naik, 2004).

Another study of in-vitro chromosomal aberration study of Caralluma extract was carried out in Human peripheral blood lymphocytes. The study was carried out in compliance with the organization of economic cooperation and development (OECD) guidelines for testing of chemicals (1997). It was concluded that Caralluma
extract is considered to be non-clastogenic in the in-vitro chromosomal aberration test (Deshmukh and Pande, 2004).

Teratogenicity study (Prenatal Development toxicity study) of Caralluma extract in Sprague Dawley rat was conducted by Intox Private Limited. This study was conducted in compliance with a study protocol, based on OECD guidelines for testing chemicals, “Prenatal development toxicity” (2001) and guidelines for developmental toxicity studies (US, FDA, 2000). The study protocol also incorporated the recommendations made in guidelines for toxicity investigations of herbal medicines (WHO, 1993). Based on the findings of the study, under Good Laboratory Practices (GLP) conditions Caralluma extract was not found to be teratogenic in Sprague Dawley rat, at the dose levels of 250mg/kg, 500mg/kg and 1000mg/kg body weight (Deshmukh and Hatarote, 2004).

Chronic toxicity study was conducted on the product to determine toxicity over long term usage, as per OECD guidelines, under GLP conditions. The study showed that NOEL (No observed effect level) for the product, following oral administration for 6 months was greater than 1000mg/kg body weight demonstrating a very high level of safety (Deshmukh et al, 2004).

Assessment of acute and subchronic oral toxicity and mutagenicity of hydroalcoholic extract of Caralluma fimbriata (CFE) in Wistar rats was performed in accordance with OECD guideline 471. Acute toxicity study revealed that LD50 of CFE is more than 5g/Kg. Sub chronic toxicity study of CFE showed no undue toxicity in either male (or) females at 90 mg/Kg, which is the recommended human equivalent dose. Hair shedding was the only adverse effect observed in male animals treated with medium (270mg/kg) and high dose (900mg/kg) and that too reversible. Loss of body weight and subcutaneous fat, as observed in medium and high dose group can be attributed to the intended use of CFE i.e., an anti-obesity dietary supplement. It is reasonable to state that the CFE is safe at human equivalent dose of 1 g/day. The no-observed-adverse-effect level (NOAEL) for rats, was found to be 90mg/kg. CFE was found to be non mutagenic in Salmonella typhimurium strains (Jag tap, 2006).

Toxicity studies on the Caralluma extracts were presented at the 2006 Annual meeting and exposition of the American Association of Pharmaceutical chemists in San Antonio, Texas, USA held from 29th October to 2nd November 2006. Caralluma fimbriata has now achieved GRAS (Generally Accepted As Safe) status and has a series of safety and pharmacokinetic studies are under way.
2.13.6 Research studies of Caralluma Fimbriata in weight reduction

A study was carried on 26 overweight patients, 19 on active compound (CFE, Caralluma fimbriata extract) and 7 on placebo, for 4 weeks. Subjects were given 500 mg Caralluma extract (one capsule) 30 minutes before a major meal. CFE showed a statistically significant reduction in body weight, and it was well tolerated. Eleven persons (61.11%) lost about six pounds. This study is suggestive of a positive effect of the Caralluma fimbriata extract on weight loss. Importantly, it reaffirmed the safety of the extract, as no serious adverse events occurred. CFE has shown long safety record with little, if any, side effects. It also significantly decrease lower blood pressure levels (Lawrence and Choudary, 2004).

A double blind, placebo controlled randomised clinical trial on Caralluma fimbriata extract was done on 50 human subjects. An extract prepared with an aqueous alcohol containing one gram of material was developed and used in the weight loss studies. The extract dosage was based upon an attempt to duplicate the average into 50 grams of raw cactus a day (10-12 grams solid material). The first study performed in India consisted of 50 overweight / obese subjects (BMI >26) of which 25 received active compound (CFE) and 25 received a placebo. The study, under the purview of the Institutional Ethics Review Board of St. John’s National Academy of Health Sciences, Bangalore, India, was randomized, and placebo-controlled, over eight weeks. The subjects were tested for weight-loss, anthropometry, body fat composition, BMI, net weight and systemic functions. During the study no changes were made in diet; and all subjects were advised to walk 30 minutes in the morning and evening. The adverse effects were minor and limited to mild upset of the gastrointestinal tract. Importantly, they were present equally in the active and placebo groups, constipation and flatulence subsided within a week and were attributed to the gelatin capsules more than the ingredients from the cactus present in the capsules. Examination of fasting and post-prandial sugar, total cholesterol, LDL, HDL, triglycerides, serum creatinine, BUN, total protein, serum albumin, total bilirubin, AST and ALT and alkaline phosphatase, gamma GT, and hemoglobin failed to reveal any overall toxicity from the extract. Blood pressure and ECG also showed no toxic reactions secondary to ingesting Caralluma fimbriata. Subjects were given 500 mg of Caralluma extract, one hour before a meal and subjects were tested for changes in key indicators of weight loss, including anthropometry, body fat composition, BMI, net weight and systemic functions. Statistically significant reductions were recorded in all key indicators of weight loss. CFE was well tolerated. CFE showed minimal adverse effects which were gastrointestinal and transient in nature (Kuriyan et al, 2007).
During the Second World Congress for Therapies against obesity, Paris 2007, Gencor Pacific presented a study on its Caralluma compound, which showed fat loss and appetite suppressant activity.

The Bharathidasan University, in India, carried an in-vitro research, showing that Caralluma inhibits progression of pre-adipocytes to adipocytes, thereby reducing the formation of new fat cells and adipose tissues. The study shows that Caralluma fimbriata extract containing pregnane glycosides at 25% concentration inhibits proliferation and impairs viability of 3 T3-L1 pre-adipocyte cells (Kamalakannan et al, 2010).

In another study, anti-obesigenic property of Caralluma was studied in male Wister rats aged 150 days, the rats were divided into 3 groups 1) Untreated control (ii) control for Cafeteria diet (to induce obesity) (iii) Cafeteria diet fed with CFE treated (at different doses 5, 10 mg, 20 mg per animal per day for a period of 90 days. The result from this anti-obesigenic study shows that CFE administration with cafeteria diet significantly reduced feed intake accompanied by considerable reduction in obesity, TC, TG, LDL and VDL and leptin by decreasing the appetite, lipogenesis, increasing lipolysis and potentially decreasing adipogenesis (Kamalakannan et al, 2010).

Serum Leptin analysis study was conducted in male wistar rats aged 120 days. They were divided into 3 groups; i) Control group (normal feed) ii) Control for cafeteria diet with vehicle for the drug treated; iii) Cafeteria diet with (CFE) treated for 90 days. Leptin level was reduced by 4.1% in CFE treated group compared to rats of 29% in placebo (Kamalakannan et al, 2010).

2.13.7 Mode of action

Caralluma fimbriata contains pregnane glycosides which are believed to block the activity of citrate lyase by acting as a competitive inhibitor. It reduces the transformation of citrate into acetyl co A, a step necessary for fatty acid synthesis in liver. Caralluma fimbriata blocks the formation of fat by the body (Preuss, 2007).

In some subjects, lipogenesis may predominate even when there is energy deficit in the food intake. Energy balance is reflected in the balance between the concentrations of carnitine acyl transferase and malonyl Co A enzyme in the cell that directly controls lipolysis and liogenesis respectively. Caralluma extracts can shift the concentration towards increased lipolysis. When Caralluma extracts are given to subjects the production of malonyl co A is inhibited leading to increase in
lipolysis and inhibition of lipogenesis. This accelerates the rate of fat loss by the body (Preuss, 2007).

Controlled clinical trials on Caralluma fimbriata extract clearly demonstrate its ability to suppress appetite. Therefore, Caralluma fimbriata is believed to have an activity on the appetite control mechanism of the brain. When we eat, nerves from the stomach send a signal to the hypothalamus in the brain. This is the part of the brain that controls appetite (Satiety centre). When the stomach is full, the mechanism signals the brain to stop eating. Further more studies have found that appetite suppression takes place without any known disturbances in the natural function of the neurotransmitter within the brain. When a person is hungry, the hypothalamus sends a signal to the brain that food is needed (Lawrence and Chowdary, 2004).

Conversely, by interfering with the signal or by creating a signal on its own, Caralluma fimbriata seems to fool the brain into thinking that the stomach is full, even when the person has not eaten. Caralluma fimbriata has been clinically demonstrated to suppress appetite and stop hunger pangs in patients. It is believed that the pregnane glycosides in Caralluma fimbriata inhibit the hunger sensor mechanism of the hypothalamus (Lawrence and Chowdary, 2004).

Most weight-loss programme fails because the patient always feels dull and tired after attaining weight loss. This makes the patient go back to his old eating habits and result in a rebound weight gain. Patients on Caralluma however, report feeling more energetic and have gained lean muscle mass, while losing fat. This is because Caralluma not only inhibits fat synthesis; it also increases the burning of fat. This makes more energy available to the body and makes the patient more active and lively (Rajendran and Venkatesh, 2007).

It is a well-known fact that muscle cells burn more calories than fat cells. So, when more energy is available to the body, muscle cells burn energy faster. The result is fat cells shrink in size and muscle becomes stronger. Muscle cells are heavier than fat cells, but they are denser than fat cells. So, they occupy less space and the patient appears trim and compact as compared to before. Patients on Caralluma have clearly shown significant decreases in arm circumference and waist circumference, along with the fat loss (Rajendran and Venkatesh, 2007).

Thus, by acting on different levels in the body’s biochemical processes and brain function, Caralluma fimbriata works as an effective appetite suppressant and
potent weight-loss agent. It helps to break down stored fat cells, particularly in those areas where cellulite tends to accumulate (Kuriyan et al, 2007).

Adipogenesis is triggered in the body when the weight increase thereof reaches the said critical point. At this stage new fat cell formation is prevented, further weight gain cannot occur and the body would shift to breakdown of excess fat in the system. This would prevent the body weight crossing the critical point (Ross et al, 2000).

Increase in fat cell numbers occurs by conversion of pre-fat into mature fat cells. Pre-adipocytes can divide but cannot store fat, while mature adipocytes store fat but cannot divide. When the fat cells in the body have taken in fat substantially to their full capacity, pre-adipocyte cell division is triggered, (Zhang et al, 2002). Caralluma fimbriata is potent a inhibitor of this cell division, reducing the number of new fat cells to be formed. This helps in decreasing fat synthesis, making it easier for our body to burn off existing fat (Zachary, 2008).

Nuclear localization of cyclin D1-CDK4/6 is critical for the G1-S transition and for the subsequent division of the cell (Lima et al, 2003). Pregnane glycosides of Caralluma extract reduces the concentration of cyclin D1-CDK4/6 in the nucleus, hence cell cycle stops and rests at G1 phase resulting in the substantial inhibition/prevention of cell division in the body (Kamalakannan, 2010).

Mixtures of pregnane glycosides exhibit synergy with regard to inhibition. Preferably, the caratubersides and boucerosides are in the proportions of about 9:1 to 19:1. The pregnane glycosides of Caralluma fimbriata interfere with and cause inhibition of cell division by interacting with one or more molecular species present or arising during the pre-adipocyte cell cycle at 25% concentration (Kamalakannan, 2010).

Studies performed on Caralluma compounds caratuberside A and B, were found to lower blood sugars in rats. Elevated blood sugar is a component of metabolic syndrome, a prevalent factor that prevents weight loss (Khan et al, 2005).

The above facts and studies clearly state that Soya and Caralluma has the potential to reduce weight. Thus Soya and Caralluma could be an effective weight reducing supplement for obese subjects.

The methodology pertaining to the above literature is discussed in the next chapter.