ANTI-PANCREATIC LIPASE ACTIVITY
OF Carica papaya Linn.

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THIS DISSERTATION IS SUBMITTED AS A PARTIAL REQUIREMENT TO OBTAIN
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INDUSTRIAL CHEMISTRY PROGRAMME
FACULTY OF SCIENCE AND NATURAL RESOURCES
UNIVERSITI MALAYSIA SABAH

2015
DECLARATION

I hereby declare that the work presented here is, to the best of my knowledge and belief, original and the result of my own investigation, except as acknowledged and has not been submitted, either in part or whole, either for any award or a degree at this or any other university. Formulations and ideas taken from other sources are cited as such. This work has not been published.

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23th June 2015
1. ASSOC. PROF DR. HOW SIEW ENG (SUPEVISOR)

SIGNATURE
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At last but not least, I also acknowledge with a deep sense of reverence, my gratitude towards my parents and member of my family, who has always supported me morally as well as economically.
Carica papaya L. contains a broad spectrum of phytochemicals, many of which show bioactivity such as anti-obesity activity. Dietary inhibitors of fats suppressing porcine pancreatic lipase (PPL) could play an important role in obesity treatment. In this study, flesh, peel and seed of C. papaya var Eksotika and Sekaki were analyzed for their total phenolic content by Folin–Ciocalteu method, antioxidant activity by 1,1-diphenyl-2-picyrlyhydrazyl radical scavenging (DPPH) and anti-pancreatic lipase activity by pH titration. The samples were prepared in ethanol, water and mixture (1:1 ethanol-water) solvent. Water extracts had the highest percentage yield compared to ethanol and mixture extracts. There were a strong correlation between antioxidant activity and total phenolic content based on Pearson correlation. The seeds extracts exhibited the highest total phenolic content and antioxidant activity, followed by peel and flesh respectively. Particularly, all samples at concentration of 0.50 mg/mL exhibited potent PPL inhibitory activity, with unripe extract of selected parts having the much stronger inhibition. Total three types unripe extracts including Eksotika flesh (mixture), Eksotika seed (mixture) and Sekaki seed (ethanol) presented the maximum inhibitory activity (> 80 %), which were lower than Orlistat as positive control (88.15 %). However, PPL inhibition was not significant correlated with total phenolic content and antioxidant activity respectively. The results demonstrated whole C. papaya could effectively inhibit the key enzymes related to obesity, especially unripe Eksotika variety had the stronger inhibition against PPL in ethanol and mixture solvent. Unripe papaya can be further applied for obesity treatment.
AKTIVITI ANTI-LIPASE PANKREAS Carica papaya Linn.

ABSTRAK

Carica papaya mengandungi spektrum fitokimia yang luas dan menghasilkan beberapa aktiviti biologi seperti anti-obesiti. Kesaran perencatan ekstrak betik dari buah, kulit dan benih ke atas aktiviti lipase pankreas telah dikaji bagi menilai potensi untuk rawatan obesiti. Tujuan dari penelitian ini juga adalah untuk memperoleh ekstrak Betik Sekaki dan betik Eksotika dalam etanol, air dan campuran (etanol- air) dalam nisbah 1:1. Pengukuran kandungan jumlah fenolik total dilakukan dengan kaedah Folin Ciocalteu dan pengukuran aktiviti antioksidan ditentukan dengan kaedah 1,1-polibrominat-2-picrylhydrazyl radikal (DPPH). Kesaran setiap ekstrak terhadap lipase pankreas dikaji berdasarkan kaedah pentitratan pH. Ekstrak air mempunyai peratusan hasil tertinggi berbanding dengan etanol dan campuran ekstrak. Secara seluruhnya, aktiviti antioksidan mempunyai korelasi yang tinggi dengan jumlah kandungan fenolik berasaskan kaedah Pearson. Ekstrak dari benih memberikan nilai tertinggi dalam jumlah kandungan fenolik dan aktiviti antioksidan, berbanding dengan bahagian kulit dan buah. Terutama sekali, tiga puluh enam ekstrak pada kepekatan 0.50 mg/mL menunjukkan perencatan lipase pancreas manakala tiga bahagian yang kurang masak mempunyai perencatan yang lebih kuat. Tiga estrak yang kurang masak daripada buah Eksotika (campuran), benih Eksotika (campuran) dan benih Sekaki (etanol) boleh dipertimbangkan sebagai perencat yang kuat, disebabkan oleh peratusan perencatanya melebihi 80 %. Tiga estrak ini menunjukkan perencatan yang lebih kurang berbanding dengan Orlistat. Walau bagaimanapun, perencatan lipase pankreas mempunyai nilai korelasi yang tidak signifikan dengan jumlah kandungan fenolik dan aktiviti antioksidan masing-masing. Keputusan ini menunjukkan seluruh betik berpotensi untuk mencegah enzim penting yang berkaitan dengan obesiti. Betik Eksotika yang kurang masak dalam etanol dan campuran pelarut boleh dikaji selanjutnya.
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<th>Definition</th>
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<tr>
<td>$\beta$</td>
<td>Beta</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>b.w</td>
<td>Body weight</td>
</tr>
<tr>
<td>CAT</td>
<td>Catalase</td>
</tr>
<tr>
<td>CaCl$_2$</td>
<td>Calcium chloride</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>$^{\circ}$C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>DPPH</td>
<td>1,1-diphenyl-1 picrylhydrazyl</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GAE</td>
<td>Gallic acid equivalent</td>
</tr>
<tr>
<td>GC–MS</td>
<td>Gas chromatography–mass spectrometry</td>
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<tr>
<td>HPLC–DAD–ESI–MS</td>
<td>High-Performance Liquid Chromatography with Diode Array Detection and Electrospray Ionization Mass Spectrometry</td>
</tr>
<tr>
<td>HPLC–MS</td>
<td>High-Performance Liquid Chromatography with Mass Spectrometry</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric acid</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>kgm$^{-2}$</td>
<td>Kilogram per square of meter</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>mL/kg</td>
<td>Milliliter per kilogram</td>
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<tr>
<td>mM</td>
<td>Milimolarity</td>
</tr>
<tr>
<td>$\mu$g</td>
<td>Microgram</td>
</tr>
<tr>
<td>MOD</td>
<td>Malonaldehyde</td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>Methanol</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometer</td>
</tr>
<tr>
<td>Na$_2$CO$_3$</td>
<td>Sodium Carbonate</td>
</tr>
<tr>
<td>NaOH</td>
<td>Sodium Hydroxide</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>-------------</td>
<td>-------------------------------------------</td>
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<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>%</td>
<td>Percentage</td>
</tr>
<tr>
<td>PPL</td>
<td>Porcine Pancreatic Lipase</td>
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<tr>
<td>pH</td>
<td>Power of Hydrogen</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>SOD</td>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td>TPC</td>
<td>Total phenolic content</td>
</tr>
<tr>
<td>TG</td>
<td>Total Triglycerides</td>
</tr>
<tr>
<td>TC</td>
<td>Total Cholesterol</td>
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<tr>
<td>vol/vol</td>
<td>Volume-to-volume</td>
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<td>WHO</td>
<td>World Health of organization</td>
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1.1 Background of Obesity

Obesity is defined as a multifactorial disease due to abnormal or excessive fat accumulation, which is relatable with many significant health problems. Such significant health problems include diabetes mellitus, hyperlipidaemia, hypertension and cardiovascular diseases (Sowers et al., 2001). Obesity can be measured by Body Mass Index is calculated as body weight in kilogram divided by the square of height in meters (Brown et al., 2000). Individual with body mass index (BMI) falls into range of 25.0–29.9 kgm\(^{-2}\) are consider as overweight, while individual with BMI exceeding 30 kgm\(^{-2}\) are considered as obese.

Overweight and obesity linked to deaths more than underweight around the world. It is the major leading cause of preventable deaths among adults and children in most developed regions such as Europe, the United States of America and Australasia. The prevalence of obesity exists even more extreme in some developing countries where the rate of increase of childhood overweight (Magarey et al., 2003). 3.4 million adults die each year because of being overweight or obese. World Health of organization (WHO) have reported that the number of obese children under age of 5 has reached 42 million in 2013 (WHO, 2014). In Malaysia, one in four is overweight or obese and the percentage of obese Malaysians is double from what it was a decade ago (Rampal et al., 2008).
Obesity is a chronic metabolic disorder that caused by exceeding energy intake over energy expenditure. Two growing issues related to caloric imbalance are individual's diet and low level of physical exercise. The fat digestion is initiated in stomach and duodenum. The colipase-dependent pancreatic lipase, which occurs in the duodenum is the key enzyme in controlling the production of fatty acids. It acts to hydrolyze triacylglycerols to produce free fatty acids, diacylglycerols, monoglycerols and glycerol. The end products of digestion are responsible for the development of obesity in body (Han et al., 2005). High-fat diet promotes excessive energy intake by passive overconsumption and weaken the fat-induced appetite control signals to prevent further consumption of fatty meal (Blundell & Macdiarmid, 1997). Improper control intake of high proportion of triacylglycerol causes excessive storage of free fatty acids in adipose tissue (Hajer et al., 2008). Enlargement of adipocytes down-regulates the control mechanisms, macrophages accumulate in the adipose tissue and inflammation arises. Oxidative stress is then happened and brings diseases to obese person.

Therefore, if the hydrolysis of triacylglycerols and absorption from the intestinal lumen into the body is stopped or minimized, the prevalence of obesity can be reduced. For this reason, an inhibitor of digestive lipases could become a useful anti-obesity agent.

1.2 Inhibitor of Pancreatic Lipase

Physical activity can elevate the average daily metabolic rate and energy expenditure to reduce body weight (Han et al., 2010). Unfortunately, this clinical approach is not long-term lasting, and weight regain is often seen. Drugs that prevent weight regain appear necessary in obesity treatment such as Orlistat which is an inhibitor of pancreatic lipase by competing with dietary fats for sites on the pancreatic lipase molecules (Astrup et al., 2009)). It have been reported that it is able to block the absorption of about 30 % of dietary fat at a therapeutic oral dose of 120 mg three times a day (Al-Suwailem et al., 2006).
Due to the side effects of synthetic drugs, the popularity of anti-obesity agents deviated from natural products is increasing, thus justifying extensive research in this field (Kovacs & Mela, 2006; Vermaak et al., 2011). The administration of secondary metabolites from natural products is potential to control obesity including catechins, mangiferin, procyaidins, proanthocyanidin and soy isoflavone (Ikeda et al., 2005; Moreno et al., 2003; Yamamoto et al., 2000). Polyphenols and saponins have been shown to be anti-oxidant agent by inhibition against pancreatic lipase to control the fatty acids absorption (Karu et al., 2007; McDougall et al., 2009). Theses natural products such as green tea, acai berries, hot pepper, soybean and *C. papaya* are effective and safe in body weight management in both human and animal studies (Gooda Sahib et al., 2012).

1.3 *Carica papaya*

*C. papaya* L. is widely cultivated in tropical regions, with demonstrated positive implications in various biological activities. Many parts are employed as medicine such as leaves, flower, roots, fruit and seeds due to high content of vitamin A, C, papain, carotenoid and phenolic compound (Zhou et al., 2011). The fruit is a powerhouse of beta-carotene (β-carotene) which can avoid the cellular damage caused by free radicals, thus it is contributed to anticancer drugs (Nguyen et al., 2013). Saponins enriched in leaves extract has been demonstrated high free radical scavenging and anticancer activity. This indicates that *C. papaya* extracts is potential to alter the growth of several types of cancer cell lines (Vuong et al., 2014).

Moreover, the antioxidant systems of *C. papaya* contribute to acceleration of wound healing and reduction of inflammation. Applying *C. papaya* leaves on the wound activates phagocytic cells to destroy bacteria (Mikhalchik et al., 2004). Major enzyme, papain found in unripe *C. papaya* fruit and leaves is evaluated in controlling edema and surgical induced inflammation (Owoyele et al., 2008; Rakhimov, 1999). *C. papaya* seeds rich in benzyl isothiocyanate exhibit effective anthelmintic properties against nematodes (Kermanshai et al., 2001). Latex from unripe fruits of *C. papaya* is examined in experimental rat models. The results show that the latex gives better protection the exogenous ulcer by lowering the acid secretion induced by intravenous infusion of histamine in chronic gastric fistulated rats (Chen et al., 1981).
*C. papaya* has a potential to control obesity and associated diseases owing to its high antioxidant of phenolic compounds and carotenoid and various biological activities such as hypoglycemia and hypolipidemia. The anti-hyperlipidemic effect of ethanolic fruit extracts is evaluated in olive oil feed rats that shows the dose-dependently inhibits the total cholesterol, triglycerides, low-density lipoproteins level and significantly increased high-density lipoprotein level (Iyer *et al.*, 2011). In addition, hypoglycemic and hypolipidemic effects of the unripe pulp extract of *C. papaya* in rats have been reported that the oral treatment on diabetic rats induce significant reduction of blood glucose and lipid profile as the dose of the extract increased (Ezekwe *et al.*, 2014). More recently, it is reported that the anti-obesity effect of the aqueous fruit extract of *C. papaya* is positive on rats fed with high fat cafeteria diet. Low calories of *C. papaya* is a promising health drink capable of modulating weight control without inducing side effects (Athesh *et al.*, 2012).

Over the past decades, the anti-obesity effect of *C. papaya* based on rats experiment has attracted great attention. Enzymatic studies of *C. papaya extracts*, however, are still at an early stage of evaluation.

### 1.4 Objectives

The objectives of this study are:

1. To prepare various extracts of *C. papaya* in ethanol, water and mixture of ethanol and water solvent.
2. To evaluate the total phenolic content and antioxidant properties of various extracts.
3. To evaluate the anti-pancreatic lipase activity of various extracts.
4. To evaluate the correlation of anti-pancreatic lipase activity, total phenolic content and antioxidant activity.
1.5 Scope of Study

The degree of inhibition of *C. papaya* L. var Eksotika and *C. papaya* L. var Sekaki were evaluated by comparing extracts from different parts of the same plant. All parts of *C. papaya* were dissolved into three different polarity solvent which were ethanol, water and mixture of ethanol and water with ratio of 1:1. Inhibitory action of the extract was significantly varied based on the solvents used for extraction. The variation was attributed with dissolving nature of the bioactive compounds in respective solvent or the polarity of the solvent was also another important factor to determine dissolving nature of active principles.

The free radical scavenging activities were determined using 1,1-diphenyl-1 picrylhydrazyl (DPPH) adapted to a microscale (Zhou *et al.*, 2011). Total phenolic content (TPC) of all extracts was performed employing the literature methods involving Folin-Ciocalteu reagent and gallic acid as standard (Slinkard & Singleton, 1977). Anti-pancreatic lipase activity was determined by measurement of fatty acids produced during the hydrolysis of substrate that was quantified by titration in the presence of pancreatic lipase. The correlation between anti-pancreatic lipase activity with antioxidant activity and total phenolic content were determined respectively.
2.1 Obesity

Obesity is currently a very threatening disease to the health of human populations with an increasing numbers of patients in both developed and developing countries. Worldwide obesity has doubled since 1980. According to WHO report in 1995, 200 million obese adults worldwide were estimated while 18 million under of five years old children were classified as overweight. As of 2000, the number of obese adults has increased to over 300 million. Besides that, over 115 million people in developing countries were estimated to suffer from obesity-related problems (Richardson et al., 1996). WHO predicted that obesity and its associated complications will attribute to two thirds of the global disease burden by 2020 (WHO, 2012).

Obesity is a metabolic disease which is defined as an accumulation of abnormal or excessive fat in adipose tissues, leading to increasing of health problem and reduced life expectancy (Garrow, 1988). Obesity can be measured with various methods, but in most studies is using BMI, defined as weight in kilograms divided by the square of the height in meters (kilogram per square meter) (Bray, 1989). The range of BMI values is suggested to monitor the condition of under-nutrition, overweight and obesity (Table 2.1) (Hedley et al., 2004).

\[
\text{BMI} = \frac{\text{Mass (kg)}}{\left[\text{Height (m)}\right]^2} \tag{2.1}
\]
Table 2.1  BMI values according to the WHO data

<table>
<thead>
<tr>
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<tr>
<td>Underweight</td>
<td>&lt;18.50</td>
</tr>
<tr>
<td>Severe thinness</td>
<td>&lt;16.00</td>
</tr>
<tr>
<td>Moderate thinness</td>
<td>16.00 - 16.99</td>
</tr>
<tr>
<td>Mild Thinness</td>
<td>17.00 - 18.49</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50 - 24.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Pre-obese</td>
<td>25.00 - 29.99</td>
</tr>
<tr>
<td>Obese</td>
<td>≥30.00</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00 - 34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00 - 39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40.00</td>
</tr>
</tbody>
</table>

(Source: Richardson et al., 1996)

Around 500 million adults worldwide are obese, which their BMI are 30 kg/m² or higher. Obesity can be further subdivided into class 1, class 2, and class 3 (BMI ≥40) to understand individual’s healthy level. The estimated total numbers of overweight and obese adults in 2005 were 937 million (922–951 million) and 396 million (388–405 million), respectively. By 2030, the respective number of overweight and obese adults was projected to be 1.35 billion and 573 million individuals without adjusting for secular trends (Kelly et al., 2008). Increasing of body fat cause higher value of BMI and rising of health risk (Garrow, 1988). In 2007, the prevalence of obesity among Malaysians aged 18 years old above has significantly raised by 28 % since the last National Health and Morbidity Survey in 1996 (Zain et al., 2007).

2.1.1  Physical and Genetic Factors

Multiple environmental factors and genetic factors trigger obesity including dietary and physical activity habits as the major reason. High fat diet with low resting metabolic rate results imbalance between energy intake and energy spent in everyday life (Bray, 1989). Increasing intake of carbohydrates releases more food energy than fat in diet. During the obesity rates in US increased, there was an increase in the average amount of food consumed (Flegal et al., 2012). Due to advanced transportation and a greater
prevalence of labor-saving technology, at least 60% of the world’s population is lack of exercise in their daily life (Ness-Abramof & Apovian, 2006).

Changes in the gene pool are limited to explain the epidemic prevalence of obesity. Single gene mutation in melano-cortin-4-receptor has been studied that it is triggered by imbalance energy. A distinct obesity syndrome that is inherited in a dominant manner is attributed by the mutation (Farooqi et al., 2003). Besides that, the rate of obesity can be increased by consumption of certain medications used to treat physical and mental illness. Patients with psychiatric disorders face higher risk of obesity than in persons without psychiatric disorders (Chiles & van Wattum, 2010).

2.1.2 Obesity Effect on Health

An obese person suffers expanses of health care at least 25% higher than a healthy person (Van Baal et al., 2008). The prevalence of obesity is associated with most common primary form of diabetes and impaired glucose tolerance. Obese adipose tissue is characterized by inflammation and macrophage accumulation. Releasing of high amount of fatty acids, glycerol and pro-inflammatory cytokines from adipose tissues enhances the development of insulin resistance. Hyperinsulinemia occurs with overstimulation of pancreatic cells and reduction of insulin receptors (Stumvoll et al., 2008). Hypertension is defined as abnormal high blood pressure related to obesity. This is due to obese characterized adipose tissue secretes bioactive molecules and immunomodulators (Hajer et al., 2008).

Indeed, the development of cardiovascular diseases is facilitated by obesity. Obesity affects the cardiac structure and heart through its risk factors such as dyslipidemia, glucose intolerance, inflammatory markers and hypoventilation. Over supply of lipid elevate the triglycerides level; and also total cholesterol. The annual sudden cardiac death rate was nearly 40 times higher in obese people than in non-obese population (Messerli et al., 1987). Abnormal heart rhythm, chest pain, angina and sudden cardiac death are attributed by obesity.
2.2 Treatment to Obesity

All weight-loss programs are required to prevent and reverse the harmful obesity-related diseases. Several treatment tools include dietary changes, increased physical activity, pharmacotherapy, diuretics and surgical treatment for obesity. The advantages and disadvantages of obesity treatment are listed in table 2.2.

Table 2.2 The advantage and disadvantages of obesity treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary control</td>
<td>Safe treatment with low calorie diets which rich in fibre, vitamins and low in fats.</td>
<td>Very low calorie diet is difficult to achieve long term weight loss since both protein and carbohydrates are still converted to fat as well (Henry &amp; Gumbiner, 1991).</td>
</tr>
<tr>
<td></td>
<td>Low calorie diets everyday can provide long-term nutrient to the obese diabetic patient</td>
<td>It causes increased uric acid level, increased risk of gall stone formation, loss of lean body mass and mild liver dysfunction (Fisher &amp; Schauer, 2002).</td>
</tr>
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<td></td>
<td>(Sacks et al., 2009).</td>
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</tr>
<tr>
<td>Physical activity</td>
<td>Low cost treatment to maintain desirable weight for long term effect.</td>
<td>Limited effect of losing weight.</td>
</tr>
<tr>
<td></td>
<td>Weight is reduced without consuming any medication.</td>
<td>Obese person prone to injuring, especially exacerbating of older adult's knee pain.</td>
</tr>
<tr>
<td></td>
<td>Compared to diet alone, moderate exercise allow greater loss of body fat versus lean muscle</td>
<td>Time consuming to succeed target weight loss (Messier et al., 2004).</td>
</tr>
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<td></td>
<td>(Healy et al., 2008).</td>
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</table>
The advantage and disadvantages of obesity treatment

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacotherapy</td>
<td>Criteria for consumption is obese person with BMI of greater than 27 and also have medical complications of obesity (Padwal et al., 2003). Weight loss is significantly increased in short term (≤1 year) include mean weight loss, percentage weight loss and proportion of patients losing ≥5% and ≥10% of initial body weight (Ioannides-Demos et al., 2005).</td>
<td>Weight gain may occur once stop taking medicine (James et al., 2000). Orlistat causes low absorption of vitamins, kidney damage and gastrointestinal side effects (oily stools, diarrhoea, abdominal pain and faecal spotting) (Filippatos et al., 2008). Side effects of sibutramine are dry mouth, inflammation of nose, constipation and increased of cardiovascular events including heart attack, hypertension, stroke and cardiovascular death prompted banning its uses in US and Europe countries (Nisoli &amp; Carruba, 2003; Woolorton, 2002).</td>
</tr>
<tr>
<td>Surgery</td>
<td>Quick, dramatic weight loss around 60% and 70 % and improvement of mental outlook without physical activity is achieved (Sjöström et al., 2007). It provide safety way to older obese patient with diabetes mellitus (Quebbemann et al., 2005; Schauer et al., 2012).</td>
<td>Rapid weight loss results formation of gallstone (Wudel Jr et al., 2002). Long term complications (anaemia, osteoporosis) are influenced by nutritional deficiencies after surgery to greater extent(Schauer et al., 2003). Others adverse effect are band slippage and erosion, pulmonary embolism, pneumonia and anastomosis leakage (Sapala et al., 2003).</td>
</tr>
</tbody>
</table>
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