Double blinded, placebo-controlled, randomised prospective intervention trial; to investigate the effectiveness of Bioslim in weight-loss and the influence of branding and advertising on the placebo response

by
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Abstract

It is estimated that 1.3 billion people worldwide are either overweight or obese, making this a global epidemic. An effective weight-loss method involves the lifestyle changes of increased physical activity and lowered energy intake. These changes are difficult to carry out and to maintain. As a result, there is a soaring demand for weight-loss aids, including dietary supplements, which exploit consumers' eagerness to find an effortless weight-loss solution. These supplements are easily accessible, require no prescription and are heavily marketed to suggest that weight loss is achievable without exercise and dieting. One such dietary supplement, Bioslim, is tested in this study.

The aim of this study was to investigate whether Bioslim results in greater weight loss than a placebo, and whether the marketing of the Bioslim brand has an influence on the placebo response.

Overweight adults residing in Cape Town (n = 87) were recruited by advertising in community newspapers and setting up stands at shopping centres. The subjects were randomised into one of four groups: Bioslim in Bioslim packaging (n = 26), Bioslim in unbranded packaging (n = 22), placebo in Bioslim packaging (n = 17) and placebo in unbranded packaging (n = 22). At baseline, the subjects were given one of the four products and anthropometric measurements (weight, height and skinfold thickness) were taken. After four weeks, these measurements were repeated. The subjects also had to complete a questionnaire regarding their experiences.

The body mass index (BMI) for the total population was 31.90 kg/m^2 (SD = 3.91) at baseline and 31.89 kg/m^2 (SD = 3.92) at follow-up. None of the measured anthropometric variables had changed significantly after four weeks. When the total study group sample was analysed, based on the allocated drug treatment groups (active or placebo), neither group showed significant weight loss from baseline to follow-up.

Twenty-three subjects from the Bioslim group and 21 from the unbranded group reported exercising during the trial. The total group's exercise time correlated significantly with fat-mass reduction (r = -0.31, p = 0.004). Furthermore, when data was analysed separately for the active and placebo groups, the active group showed a significant correlation (r = -0.45, p = 0.0012), while the placebo group showed an insignificant correlation (r = -0.05, p = 0.77). The same was not reflected in weight loss (r = -0.007, p = 0.95).

It is concluded that Bioslim is an ineffective weight-loss supplement: subjects receiving active pills evidenced no significant beneficial changes in weight, waist circumference or body composition. More than half of the subjects attempted dieting and exercising, but these efforts were insufficient to impact on weight loss. The marketing and packaging of Bioslim did not enhance the placebo effect.

One subject from the active group withdrew from the study, complaining of severe headaches and heart palpitations. There was no difference in adverse events reported by the remaining active and placebo group subjects.

In conclusion, this study emphasises the need for better regulation of the efficacy and safety of dietary supplements.

Opsomming

Daar word geskat dat 1.3 biljoen mense wêreldwyd oorgewig of vetsugtig is, wat dit 'n globale problem maak. 'n Effektiewe gewigsverlies metode inkorporeer leefstyl veranderinge soos verhoogde fisiese aktiwiteit en 'n laer energie inname. Hierdie veranderinge is moeilik om uit te voer en vol te hou. Die gevolg is 'n stygende aanvraag vir gewigsverliesprodukte en supplemente, wat verbruikers se gretigheid om 'n maklike gewigsverlies oplossing te kry, uitbuit. Hierdie supplemente is maklik verkrygbaar sonder 'n voorskrif en word aggressief bemark met bewering dat gewigsverlies moontlik is sonder oefening en dieetaanpassing. Een van die beskikbare produkte, Bioslim, is getoets in die studie.

Die doel van die studie was om te ondersoek of die gewigsverlies produk, Bioslim, lei tot 'n groter gewigsverlies as 'n plasebo produk en of die bemarking van die Bioslim handelsmerk 'n invloed op die plasebo-effek het.

Oorgewig volwassenes woonagtig in Kaapstad (n = 87) is gewerf deur advertering in gemeenskapskoerante en deur stalletjies by inkopiesentrums. Die proefpersone is ewekansig in vier groepe ingedeel: Bioslim in Bioslim verpakking (n = 26); Bioslim in verpakking sonder 'n handelsmerk (n = 22); 'n plasebo produk in Bioslim verpakking (n = 17) en 'n plasebo produk in verpakking sonder 'n handelsmerk (n = 17). Met aanvang van die studie is een van die vier produkte aan die proefpersone gegee en antropometriese metings (gewig, lengte en velvoudikte) is gemeet. Metings is na vier weke herhaal. Die proefpersone moes ook 'n vraelys oor hul ervarings voltooi.

Die liggaamsmassa indeks (LMI) van die totale populasie was 31,90 kg/m^2 (SD = 3.91) by basislyn en 31.89 kg/m^2 (SD = 3.92) met opvolg. Geen van die antropometriese veranderlikes het betekenisvol verander na vier weke nie. Met ontleding van die totale studie polulasie, gebasseer op die toegekende behandeling (aktiewe of plasebo bestanddele), is gevind dat geen groep 'n betekenisvolle gewigsverlies getoon het van basislyn tot opvolg nie.

Drie-en-twintig proefpersone uit die Bioslim groep en 21 uit die geen-handelsmerk-groep het gerapporteer dat hul geoefen het gedurende die studie. Die totale groep se oefenings tydsduur het betekenisvol gekorreleer met 'n verlaging in vetmassa (r = -0.31, p = 0.004). Met verdere analiese van die data in die aktiewe en plasebo groepe, is gevind dat die aktiewe groep 'n betekenisvolle korrelasie getoon het (r = -0.45, p = 0.0012), maar die plasebo groep nie (r = -0.05, p = 0.77). Hierdie bevinding is nie gevind in die gewigsverlies nie (r = -0.007, p = 0.95).

Die gevolgtrekking word gemaak dat Bioslim 'n oneffektiewe gewigsverlies supplement is, aangesien proefpersone wat die aktiewe pille geneem het, geen betekenisvolle voordelige veranderinge in hul gewig, middelomtrek of liggaamsamestelling getoon het nie. Alhoewel 'n betekenisvolle korrelasie gevind is tussen oefeningsduur en verlies aan vetmassa in meer as die helfte van die proefpersone, was die omvang daarvan onvoldoende om 'n impak op hul gewigsverlies te hê. Die bemarking en Bioslim handelsmerk het nie die placebo-effek versterk nie.

Een persoon uit die aktiewe groep het van die studie onttrek as gevolg van erge hoofpyn en hartkloppings. Daar was geen verskil in die nadelige effekte gerapporteer deur die oorblywende proefpersone in die aktiewe en plasebo groepe nie.

Ten slotte beklemtoon die studie die behoefte aan beter regulering van die effektiwiteit en veiligheid van dieetsupplemente.

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<u>Contributions by principal researcher and fellow researchers</u>

The principal researcher (Tina Lee) developed the idea and the protocol. The principal researcher planned the study, undertook data collection with the help of a research assistant (Nai-Jen Hsu), captured data for analyses, analysed the data with the assistance of a statistician (Prof DG Nel), interpreted the data and drafted the thesis. Dr H Steinman and Mrs I Labuschagne provided input at all stages and revised the protocol and thesis.

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List of Abbreviations

ASA – Advertising Standard Authority of South Africa

AI – Adequate Intake

BIA – Bioelectric Impedance Analysis

BMI – Body Mass Index

LMI – Liggaamsmassa Indeks

CHD – Coronary Heart Disease

DSHEA – The Dietary Supplement Heath and Education Act

DXA – Dual-Energy X-Ray Absorptiometry

FDA - Food and Drug Association

OTC – Over-the-Counter

MCC – Medicines Control Council

MRA - Medicines and Related Substances Control Act

MRI – Magnetic Resonance Imaging

NHANES - National Health and Nutrition Examination Survey

NIH – National Institute of Health

RDA – Recommended Daily Allowance

UWW – Underwater Weighing

WHO- World Health Organisation

WISE – Women's Ischemia Syndrome Evaluation

Chapter 1

Literature Overview

1.1 Overweight and obesity

1.1.1 An overview of overweight and obesity

According to the World Health Organisation's (WHO) classification, an individual is overweight if their body mass index (BMI) is greater than or equal to 25kg/m^2. If it is greater than or equal to 30kg/m^2, they are classified as obese [1]. Physiologically, an individual becomes overweight when the energy expended is less than the energy consumed. The excess energy is then stored as triglycerides in the adipose tissue and weight is gained [2]. However, overweight and obesity is a complex issue, influenced by multiple factors such as culture, behaviour, environment, genetics and metabolism [3].

It is estimated that 1.3 billion people worldwide are either overweight or obese, which makes it a global epidemic [4]. The greatest prevalence of overweight and obese individuals is found in developed countries such as the United States (where 65% of adults are either overweight or obese, according to the 1999-2002 National Health and Nutrition Examination Survey result [5]). However, it is also a major concern in developing countries.

In South Africa, the problem is amplified by the double burden of under-nutrition and chronic diseases of lifestyle. The overall prevalence of overweight and obesity is relatively high compared to other African countries, with more than 29.9% of men and 55% of women in South Africa being classified as overweight or obese [6]. Indian women have the highest prevalence of overweight and obesity (59.2%), with slightly lower levels among Black African women (56.2%), Coloured women (52.2%) and White women (38%). Among males, White men have the highest prevalence (48%), followed by Indian men (45%), men of mixed ancestry (36%) and lastly, Black men (27%). Besides ethnicity, such high prevalence is also associated with age, low level of education and degree of urbanisation [6].

The phenomenon of the double burden is also seen from the 2005 NFCS (National Food Consumption Survey) data [7]. The cross-sectional survey showed that 5.04% of children between the ages of 1-9 years were obese and 17.12% were overweight. A significant difference in prevalence was found between rural and urban areas, as well as between age groups. The highest prevalence was found in urban areas and in children between the ages of 1-3 years. These data indicate that nutrition transition is taking place in the urban areas and that under-nutrition, which is associated with infectious diseases, is not the only concern for children any longer. Furthermore, the prevalence of stunting (19.3%) is similar to the combined prevalence of overweight and obesity (22.16%) of children between the ages of 1-8 years old in SA. Additionally, stunted children are predisposed to become overweight adults

when adequate nutrition is available, which further increases the risk of children becoming obese adults [7].

A follow-up survey, conducted in 2005, found that on a national level, 10% of children aged 1-9 years were overweight and 4% were obese. Stunting and underweight still remains the most common of nutritional disorders, since 20% of the children are stunted and 10% are classified as underweight [8].

The most recent national data indicate that the combined national prevalence of overweight and obesity among women is 51.5% with the highest provincial prevalence in the Western Cape (58.7%) [8].

1.1.2 Consequences of overweight and obesity

1.1.2.1 The effect of overweight and obesity on physical health

Obesity is listed by the WHO as one of the ten leading risk factors for mortality [9]. There is a general consensus that obesity (BMI > 30), as well as overweight (BMI> 24.9), increases the risk of a number of major chronic diseases or conditions including insulin resistance, hyperlipidaemia, hypertension and stroke, type 2 diabetes, and cardiovascular disease, as well as cancers of some sites [4].

Globally, non-communicable diseases caused an estimated 35 million deaths in 2005 which represents 60% of all deaths. Eighty per cent of these deaths occur in low- and middle-income communities and it has been predicted that deaths from non-communicable diseases will increase by a further 17% over the next 10 years. Furthermore, the rapidly increasing incidence of these diseases is affecting poor and disadvantaged populations disproportionately, causing enormous human suffering and threatening the economies of many countries, as they impact on the older and experienced members of the workforce [4].

1.1.2.2 Heart diseases

Overweight and obesity increase the risk of developing coronary heart disease (CHD), where excess weight increases various cardiovascular risk factors such as hypertension, high blood-lipid concentrations and type 2 diabetes mellitus. CHD is reported to have a linear relationship with BMI, and from the Framingham study it is estimated that a 10% loss of weight can reduce the risk of CHD by 20% [10].

Obese individuals invest more effort in breathing due to the excess weight on the chest, which requires the heart to work harder in order to pump adequate amounts of blood into the lungs

and throughout the body for good perfusion. It is also common to find left ventricular hypertrophy in obese individuals as the left chamber of the heart is responsible for the pumping of blood throughout the body. Eventually this can lead to heart failure and a heart transplant would be required [10].

Not only is the heart working harder to cope with the excess body weight, but a high fat dietary intake can also result in a poor lipid profile. Elevated levels of cholesterol and lipids in the blood can easily cause plaque and the narrowing of the blood vessels. This may eventually lead to a number of vascular complications where the supply of blood and oxygen is restricted due to a blocked artery. These vascular complications include ischemic heart disease such as myocardial infarction, or cerebrovascular incidents in which the blood supply to the brain is hindered due to a burst vessel. Both of these complications have a high mortality rate, and heart disease is currently the leading cause of death in the western world with stroke coming third in the ranking, responsible for 10% of deaths worldwide each year [11]. According to the World Health report by the WHO, cardiovascular disease accounts for 9.2% of all deaths in African countries. In South Africa, specifically, 195 people die from cardiovascular diseases (CVD) every day [12].

1.1.2.3 Type 2 diabetes mellitus

An increase in weight is strongly associated with the risk of developing type 2 diabetes mellitus, as it is related to excess intake of calories and insulin resistance. Constant high levels of blood glucose require additional insulin to be produced by the pancreas. Over time, this desensitizes the cells to the constant high insulin levels and individuals may become pre-diabetic. Eventually, with the continuing death of beta cells, the pancreas can no longer produce the required amount of insulin to stabilize postprandial hyperglycaemia to normal blood glucose levels [10].

This is further verified by a prospective study by Hu *et al.* [10], which showed that overweight and obesity was the most important predictor of diabetes. 91% of the subjects who developed diabetes during the study period can attribute it to poor diet and lack of exercise. From a meta-analysis study, it has been shown that the incidence rate ratio (IRR) for obese men was 6.74 and for obese women was 12.41 (BMC public health). It was estimated in 2000 that 1.5 million South Africans are diabetic and that 3% of men and 6% of women over the age of 30 die from diabetic-related complications [12].

1.1.2.4 Gallstones

An increased risk of developing gallstones is associated with an increase in weight. It was found that the risk increased by nearly 7 times when comparing normal weight women to obese women [13].

1.1.2.5 Osteoarthritis

Epidemiological studies have shown that as BMI increases, so does the prevalence of knee and finger osteoarthritis. The increase in prevalence cannot be solely attributed to the additional stress brought on by excess weight; metabolic disturbances of the cartilage that are associated with obesity also play a role. This view is supported by the evidence that osteoarthritis of the finger, which is not impacted by mechanical stress, also occurs more frequently in obese individuals. Additionally, a drop of BMI by 2 units can reduce the risk of osteoarthritis by more than 50% [14].

1.1.2.6 Cancer

Various prospective and retrospective studies have also shown that obesity and overweight are strongly associated with cancer of the colon, rectum, breast, ovaries and endometrium [15]. For colon cancer, the risk profile for men and women is similar, as for both; an increase in BMI is related to an increased risk of colon cancer. A high waist-to-hip ratio specifically, is a strong independent predictor [16].

From the epidemiologic studies, it is suggested that obesity correlates strongly to breast cancer, specifically in postmenopausal women who are not receiving hormone replacement therapy. In postmenopausal women, the peripheral fat produces oestrogen and the higher the level of oestrogen production, the greater the risk of breast cancer. It has been shown that the breast cancer incidence rate ratio for overweight women is 1.13 and increases to 1.3 for obese women [16].

1.1.2.7 Women's reproductive health

Premenopausal obese women may experience an irregular menstrual cycle or amenorrhea and this in turn can lead to infertility. From the Nurse's Health Study, it was found that the greater the BMI at the age of 18 years, the greater the risk of ovulatory infertility [17, 18].

During pregnancy, higher pregnancy weight is associated with higher incidences of late foetal death and gestational diabetes, which can result in complications during delivery. In obese pregnant women, the prevalence of hypertension increases by 10 times and there is a 10% increase in the risk of developing diabetes [17, 18].

Seven overweight and obesity related co-morbidities have been summarised in Table 1.

Table 1: Physical morbidities that are related to overweight and obesity

Health Problems	Relative risk
Hypertension	It is threefold more likely for overweight and obese adults (between the ages of 20-75) to develop hypertension than normal weight individuals [19].
Hypercholesterolemia (>6.7mmol/L)	1.5 times higher risk in obese individuals than lean counterparts [20].
Diabetes Mellitus	Adults with a BMI of 40 or higher are 7.37 times more likely to develop diabetes than adults with normal weight [10].
Gallbladder disease	Gallstones are 4 times more likely to be found in obese than normal weight individuals [21].
Gout	2.6 times more likely for obese individuals compared to normal weight individuals [22].
Cancer	For individuals who are 40% or more overweight, there is an increased risk of cancer: 1.33 times in men and 1.55 times in women [16]. Specific cancers related to obesity in men include prostate, stomach, oesophagus, liver, rectum and colorectal cancers. For women, the list includes gallbladder, uterus, kidney, colon, rectum, gallbladder, liver, cervical, ovarian and breast cancer [15].
Sleep disorder breathing (including sleep apnoea)	Obese adults are 10 times more likely to develop sleep apnoea [23].

1.1.2.8 The cost of overweight and obesity

In addition to the increased risk of co-morbidities, overweight and obesity place a heavy burden on healthcare systems at both government level and in the private sector. The United States' direct cost for treating obesity-related illness has been estimated at $51.6 billion per year, which equates to 6-7% of the country's National Health Expenditure. The money spent specifically on weight reduction amounts to well over $30 billion [24]. One study indicated that the number of medically diagnosed illnesses and the need for healthcare resources increased as BMI increased [25]. Another study analysed the employees of 298 companies (n = 8822); the obese subjects from this study generated a significantly higher healthcare cost compared to

their non-obese colleagues when adjusted for age, sex and chronic health conditions [26]. As previously mentioned, one of the common morbidities related to overweight and obesity is cardiovascular disease; the direct cost of CVD in South Africa is between R4.1 - R5 billion or roughly 25% of all healthcare expenditure. An increasing number of the work-force population aged 35-64 years is lost to CVD, which has a serious impact on the country's economy [27].

1.1.2.9 The psychological effect of overweight and obesity on an individual's self-esteem and self-image

It has been well established by various studies [28] that women's perception of their body image has been profoundly influenced by Western culture via the media's constant contention that the ideal body shape is slender [29]. Success and happiness are associated with slender women and conversely, being overweight is stigmatised as lazy, unattractive, unsuccessful and physically unhealthy [30]. According to Callaghan [31], *Self-esteem is greatly affected if one learns to value oneself through the eyes and values of society*. Hence, as an overweight individual in the Western culture, it is easy to internalise these negative opinions from the media and to develop a poor body image perception, and as a result, lower one's self-esteem. It intensifies the urgency to work hard on weight-loss and to try a variety of methods to lose weight in order to achieve the acceptance of society, and to improve self-esteem by dissociating oneself from the negative connotations of being overweight. Such body image dissatisfaction may not be satisfied by weight loss attempts, however, as the goal is often unrealistic. This is partly due to the media's promotion of very skinny-looking women and partly due to advertisers promoting the false belief that it is easy to reach these goals. The unrealistic goals may only lead to unsuccessful weight loss attempts and intensify the sense of failure, increasing the frustration of obese individuals and further impairing their self-esteem.

A high incidence of eating disorders provides further indication of the increased pressure from society to push individuals into being slender [32].

However, in black communities, the incidence of eating disorders was previously considered rare, as the cultural perception of overweight was related to affluence, health and, for women, fertility [33]. Overweight black women are resistant to weight-loss and adopting healthy lifestyle behaviours as weight-loss is associated with HIV/AIDS and wasting syndrome [34]. This cultural perception is gradually diminishing as westernisation of the community takes place. Black females are now adapting to the new perceived ideal body shape, and the same pressure from society to be slender is being applied [35]. According to Freud [36], body image is the individual's subjective sense of the body and is theorized to be a core component of

personality. In addition, Fisher [35] states that body image is a result of socio-cultural values and social responses to body appearance and a continuous body-related experience. These self-images are established at a young impressionable age and media can have a profound effect on them. It was found that obesity in children is the most stigmatised and the least socially acceptable condition [37]. As a study [37] has shown, normal weight children ranked obese children as the least desirable friends, as they are perceived as lazy, dirty and unintelligent. These descriptions are from children as young as 6 years old. As a result, obese children feel excluded from social activities and easily become targets for teasing. Consequently, obese children are often found to have a lower self-esteem and tend to miss school four times more often than normal weight children, leading often to poor performance in school [38].

These social influences during childhood have a lifelong effect on the individual, as it has been found that obese children who grow up as obese adults, tend to have a lower education level, less income and are less likely to be married [37].

Being overweight has psychological as well as physiological effects. Overweight and obese individuals are discriminated against in work, social and healthcare settings [26]. Studies that investigated workplace prejudice showed that participants hold negative stereotypes of overweight individuals, including a lack of self-discipline, a poor professional appearance and low supervisory potential [39]. Similar results were found in a medical setting [40].

Results from a study of general practitioners, using anonymous questionnaires, reported that 66% thought their obese patients lacked self-control and 39% thought they were lazy. This is worrisome; while physicians recognise the health implications of obesity, few of them discuss the importance of weight management with their overweight patients [40]. Salinas *et al.* [41] reported that although physicians believed obesity can be managed successfully, they do not feel confident in their ability to do so. Only physicians who have greater knowledge, a positive attitude and more time available to spend on weight management, would consider providing counselling to their obese patients. This lack of medical support further exacerbates the problem of overweight and obesity by forcing patients to use non-substantiated and often inappropriate commercial assistance [41].

1.2. Overview of treatment options for overweight and obesity

Due to the alarmingly high prevalence of overweight and obesity, a search for a treatment that is effective, sustainable and with acceptable side effects is essential. There are several treatment options available for weight loss and the decision regarding which treatment option to use should be based on the individual's degree of overweight and weight-loss history.

1.2.1 Lifestyle intervention for obesity

This is the most cost-effective intervention, but one that requires the most effort from the individual, as this intervention includes a restricted energy diet and exercise. Table 2 displays 7 trials that have studied the effectiveness of lifestyle interventions over 1.5 years and how sustainable they were in order for subjects to maintain their weight loss. It was found that in all 7 trials the treatment group lost significantly more weight than the placebo group. All trials included a follow-up meeting after treatment had been completed, where physicians kept regular contact with the subjects to provide support. These follow-up meetings were found to be the pivotal factor in the maintenance or the continuation of the weight loss. On average, 60-80% of the weight loss could be maintained with bi-monthly contact after the treatment phase [42].This treatment option for overweight and obesity is one with minimal risk and side effects, though it does require commitment from subjects for the success of the intervention. It is something that is often considered a formidable task.

Table 2: Randomised trials that investigate the effectiveness of lifestyle intervention [42]

Research group	p - value	Total sample size	Follow-up period (years)	Weight change at the end of the trial (kg)	
				Treatment	Placebo
Diabetes prevention program [43]	$p < 0.01$	3224	2.8	-5.6	-0.2
Finnish Diabetes Prevention [44]	$p < 0.01$	522	3.2	-3.5	-0.8
TONE [45]	$p < 0.01$	585	2.5	-4.7	-0.9
Da Qing IGT Study [46]	$p < 0.05$	332	6.0	-1.8	0.3
Hypertension Control Program [47]	$p < 0.01$	189	4.0	-1.8	2
MRFIT [48] [1]	$p < 0.01$	12866	6-8	-0.5	0.3

[1] Multiple Risk Factor Intervention for the Prevention of Coronary Heart Disease

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1.2.2 Behavioural therapy for obesity

Behavioural therapy coaches individuals to develop a set of skills for healthy eating. Behavioural therapy is based on classical conditioning where eating is assumed to be prompted by cues which are linked to food. Hence, weight loss can be promoted by helping subjects to develop new responses when facing triggers relating to eating [49].

Short-term results have shown that subjects had a mean weight loss of 9.6kg after 21 weeks of therapy [50], and similar results were found in other studies [51, 52, 53].

Behavioural therapy is often combined with other treatment options such as pharmacotherapy. Wadden *et al*. [54] have shown that pharmacotherapy with behavioural therapy resulted in the most weight lost (17.7% of baseline weight) when compared to groups that received only weight-loss drugs or behavioural therapy. The combined treatment group also maintained most of the weight loss at 1 year. Results from a systematic review showed that behaviour therapy coupled with Sibutramine led to weight loss that was maintained for up to 18 months [55].

1.2.3 Bariatric surgery for obesity

Bariatric surgery includes procedures such as gastric banding, gastric bypass and duodenal switch, and is indicated for individuals who are morbidly obese with the BMI > 40 or ≥ 35 with co-morbidity according to NIH (National Institute of Health) [56]. According to a systematic review and meta-analysis study, bariatric surgery can markedly reduce co-morbidities such as type 2 diabetes, hypertension and hyperlipidaemia post-surgery [57]. However, adverse effects after surgery are common with 7 - 8% of the patients suffering from severe side-effects such as sub-phrenic abscess, pneumonia and wound infection. The mortality rate for such surgery is considered low, between 0.5 - 1% [42].

Bariatric surgery is an effective weight loss intervention, although one needs to consider the cost-effectiveness of the surgery and regard it as the last option when all other non-surgical interventions have been attempted, and have failed.

1.2.4 Pharmacotherapy for weight loss

According to the FDA's estimation, 50 million Americans go on diet each year by joining weight-loss programmes or making use of weight-loss drugs, but only 5% maintain the lost weight, if any weight was lost to begin with [58]. Pharmacotherapy is one of the most popular choices of treatment for overweight and obesity as it requires the least amount of effort from

individuals. Although an effective and safe weight-loss drug is highly desirable, there is not one currently available without undesirable side effects and careful consideration is therefore required before the commencement of this treatment option. The drug's benefits regarding weight loss must be weighed up against its side effects and correct usage of such drugs must be ensured to avoid abuse. Anti-obesity drugs are available to the public in two ways: as prescribed medication and as an over-the-counter dietary supplement. The benefit of prescribed medication is that drugs are tested for efficacy and possible side effects via scientifically sound clinical trials. (Table 3 is a summary of the clinical trial criteria used when conducting a drug efficacy and safety trial.) However the same does not necessarily apply to over-the-counter dietary supplements.

Table 3: Criteria for anti-obesity drugs to ensure efficacy according to the Food Drug Administration (FDA) and Committee for Propriety Medicinal Products (CPMP) [59]

	FDA criteria	CPMP
Initial trial		
Type of trial	Randomised, double blinded, placebo-controlled dose ranging: for identification of the lowest effective dose	Not specified
Duration	3 - 6 months	Not specified
Subject type	BMI >30 kg/m^2	
End result	Weight loss is significantly greater in the treatment group than placebo group	Weight that was lost is mostly fat mass
Long-term trial		
Type of trial	Randomised, double blinded, placebo-controlled dose ranging: for identification of the lowest effective dose	12 months, open label or random 24 weeks for efficacy and safety
Duration	2 years	Minimum 1 year
Subject type	BMI >30 kg/m^2 otherwise healthy Or BMI >27 kg/m^2 with co-morbidities	BMI >30 kg/m^2 otherwise healthy Or BMI >27 kg/m^2 with co-morbidities
End Result	Weight loss is significantly greater than placebo. At 12 months, it should be higher than 5% when compared to placebo group. Such weight loss is maintained.	Loss of 10% of the baseline weight and significantly greater than placebo group at 12 months.

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1.2.4.1 Prescription drugs

Prescription weight-loss drugs require careful selection for individuals, for whom the treatment is appropriate, in order to avoid abuse. Such individuals should have a BMI > $30kg/m^2$, or have a BMI of $27kg/m^2$ and also suffer from other weight-related co-morbidities such as dyslipidaemia, hypertension, sleep apnoea or diabetes. Individuals are often required to use these drugs as a long-term therapy and they are treated like any other chronic disease drugs, such as lipid-lowering or anti-hypertensive medication. One should aim for a loss of 15% of the original weight after three to six months on the prescribed medication [60].

Weight-loss drugs can be grouped in three main categories: 1) reducing food intake, 2) altering the metabolism of macronutrients and 3) increasing energy expenditure. Examples of drugs that have been approved by the FDA for reduction of food intake are Phentermine, Mazindol and Sibutramine. Orlistat has been approved for inhibiting the absorption of gastrointestinal lipase, which is essential for the breakdown of triglycerides to free fatty acid hence preventing fat absorption. There are currently no FDA-approved weight-loss drugs to increase energy expenditure. Ephedrine has been banned for weight-loss purposes, due to its dangerous side effects, although some studies have shown that it is effective when used together with caffeine to stimulate thermogenesis [61]. See Table 4 for the list of FDA approved drugs, together with the results of their efficacy from a systematic review.

Table 4: List of drugs approved by the FDA for weight-loss purposes [62, 63].

Generic Name	Trade Name	Efficacy	Notes: adverse effects, original purpose, drawbacks
Approved for long-term treatment			
Orlistat	Xenical	Treatment group lost 2.9kg, 2.9% (significantly more) than placebo group.	Possible gastrointestinal (GIT) side effects. Results from systematic review showed that 80% of participants experienced GIT side effects such as faecal urgency, oily stool and oily spotting.

Sibutramine	Meridial, Reductil	Treatment group lost 4.2 kg, 4.3% (significantly more) than placebo group.	Raises blood pressure: systolic blood pressure by 1.7 mm Hg and diastolic blood pressure by 2.4 mm Hg. May not be appropriate for subjects with hypertension. Other side effects: Nausea, dry mouth, constipation, insomnia.
Rimonabant	Accomplia	Treatment group lost 4.7kg more weight than placebo group.	Mood swings and gastrointestinal side effects. Contraindicated for subjects on anti-depressants. 6% of the subjects in the treatment group experienced serious adverse events (depression, anxiety, irritability and aggression) compared to 4% of the subjects in placebo group.
Approved for short-term treatment (up to 12 weeks)			
Phentermine	Bontril	Only short-term studies are available and weight loss was significantly more in treatment group.	Long-term use may promote tolerance, prompting an increase in the dosage of drug.
Diethylpropion	Tenuate, Tepanil		Same as above.
Mazindol	Mazanor		Appetite reducing effects decrease after a few weeks of using Mazindol, hence not effective for long-term use.
Approved for other purposes, but have the effect of promoting weight-loss			
Metformin	Glucophage	Not indicated for weight loss.	Used for diabetic treatment
Bupropion	Wellbutrin		Used as an antidepressant
Zonisamide	Zonegran		Antiepileptic
Topiramate	Tomapamax		Antiepileptic

Although the FDA approves the drugs listed in Table 4 for their efficacy and tolerable side effects, they are not the first line of treatment for overweight and obese individuals. There are recommended treatment plans by the National Institute of Health [64] that suggest one should start treatment with diet modification and exercise and only move onto pharmacotherapy once these interventions show minimal or no effect on weight loss. In addition, while these drugs

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may have an effect on weight loss during the treatment period, weight regain is common at the cessation of therapy; subjects still require alternate therapy to avoid weight cycling.

If one considers obesity as a clinical disease, there are currently no cures for it. Weight loss drugs can be a temporary effective solution for some or can be used as an adjunct to other core therapies that involve lifestyle intervention.

1.2.4.2 Over-the-counter (OTC) medication / dietary supplements

There are a great number of OTC weight-loss products currently available on the market and this is mostly due to the ease with which products are allowed to appear in the market without adhering to stringent regulations, as well as popular demand from the consumers. See below for a list of reasons for using dietary supplements. Such products are appealing to the general public, as they are often reinforced by attractive marketing schemes. Intensive advertising often suggests the product's effectiveness via simple testimonials, which have no scientific basis. While the prevalence of obesity is increasing at an alarming rate, the general public does not consider it as a disease. Instead, people associate it with laziness and lack of willpower [65]. As a result, there is a lack of urgency to seek medical professionals' help, leading many consumers to purchase one of the easily accessible products that make up the multi-million rand market. Box 1 lists the reasons that consumers turn to using dietary supplements.

Box 1:Reasons for using dietary supplements [65]

Reasons for using dietary supplements
- Belief that they are effective
- There is a stigma associated with overweight and obesity
- Benefit of a healthier body
- Consumers desire a quick and easy fix
- Requires less effort from the consumers compared to exercise and lifestyle changes
- Failure of previous attempts at exercise and/or dieting
- Easily accessible as they do not require a prescription
- Attractive advertising claims
- Perception that the product is safe as most products claim to be natural substances

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South Africans are currently spending over R900 million a year on dietary supplements, including vitamin and mineral supplements, weight-loss drugs and body-building supplements [66]. The demand for natural herbal supplements is expanding due to the public's increased awareness of health products, fitness centres which advocate them, recent publications on the importance of nutrition in health and effective marketing programmes.

As popular as these products are, most lack clinical data to support their effectiveness. Therefore, a moderate side effect can easily shift the risk-benefit ratio and discourage the use of such products.

1.2.4.3 Bioslim

In this study, we have chosen to investigate Bioslim as an example of one of the many products available on the market which is also vigorously promoted (it claimed at one time to have a 51% market share of this class of products) [67]. It is one of the dominant weight-loss products on the market and is easily accessible to consumers without prescription. Several randomised controlled trials have taken place to study some of the individual active ingredients contained in Bioslim, with no robust evidence having shown any to be efficacious in weight loss at the doses tested in those studies [68, 69]. However, as is the case with many other weight-loss products, no clinical trial has been done that tests the entire product's effectiveness as a weight-loss drug.

Table 5 lists the ingredients comprising Bioslim Once a Day. Pyruvate and *Citrus aurantium* are the two key ingredients found in Bioslim Once a Day, and the daily dosage is roughly 230mg and 200mg respectively.

Table 5: Ingredient list in each of the 3 capsules found in Bioslim Once a Day

Loss Accelerator – each capsule contains (One tablet per day for the next 7 days)	
Calcium pyruvate	200mg
Citrus aurantium	150mg
Gotu kola	100mg
Guarana	50mg
Ginger root	48mg
Cascara sagrada	30mg
White Willow Bark	20mg
Garciniacambogia	15mg

Slimtone – each capsule contains (One tablet per day for the next 28 days)	
L'CarnitineFumarate	80mg
Citrus aurantium	50mg
Calcium pyruvate	30mg
Botanical Herb Blend	25mg
Calcium Ascorbate	1.25mg
Pyrodoxine as HCl	333mcg
Chromium as Picolinate	16mcg

Nutri-Vitamin – each capsule contains (One tablet per day for the next 28 days)		% RDA/AI [70] contribution for adult female	% RDA/AI [70] contribution for adult male
Ascorbic Acid	55mg	73%	61%
Botanical Herb blend	55mg	-	-
Prune concentrate	50mg	-	-
Magnesium	40.4mg	12.6%	10.1%
Choline Bitartrate	24mg	-	-
Nicotinic Acid (vit. B3)	12.6mg	90%	78.75%
Kelp Powder (deiodised)	12.4mg	-	-
Citrus Bioflavanoid	8.4mg	-	-
Inositol	8.4mg	-	-
Vitamin E (α - TE)	7.2mg	48%	48%
Calcium Pantothenate (vit. B5)	5.5mg	110%	110%
Calcium	4.6mg	0.46%	0.46%
Zinc	4mg	50%	36.36%
Pyrodoxin HCl (vit. B6)	2.51mg	167%	193%
Vitamin B1	2mg	182%	166%
Vitamin B2	1.8mg	163%	138%
Manganese Glycerophosphate	1.7mg	34%	34%
Ferrous	130mcg	0.72%	1.63%
Vitamin A (RE)	69mcg	0.01%	0.01%
Folic Acid	67mcg	0.02%	0.02%
Chromium as Picolinate	67mcg	0.27%	0.19%

D-Biotin	50mcg	0.17%	0.17%
Potassium	17mg	0.36%	0.36%
Copper	8mcg	0.88%	0.88%
Vitamin B12	3mcg	0.13%	0.13%
Cholecalciferol (vit. D3)	0.03mcg	0.00%	0.00%

Analysis of the Bioslim ingredient list shows that although some of the micronutrients, such as Vitamins B1, B2, B5 and B6, exceed the Recommended Daily Allowance[2] (RDA), none of them exceed the Upper Limit (UL) where the UL figure is available.

Ingredients such as pyruvate and L'Carnitine, which claim to increase fat oxidation and reduce fat synthesis [71, 72], have shown minimal or no effect in studies, or their effectiveness has not been conclusively confirmed. Where there is some evidence of possible efficacy, the dosage used in this product is questionable. For example, studies of pyruvate have shown minimal effect on weight loss when subjects consume 6g per day divided over 3-4 doses per day. However, Bioslim claims its effectiveness using only 2.3g of pyruvate once per day [72]. In one study, Guarana extract (*Paulliniacupana*), used in conjunction with ephedra, has shown short-term effectiveness in weight loss, but no study of Guarana on its own has shown any effectiveness [73].

The ingredient, *Citrus aurantium*, otherwise known as bitter orange, which is similar to ephedra, contains an adrenergic agonist such as synephrine alkaloids. Ingesting 50mg of synephrine has the potential to raise systolic blood pressure, diastolic blood pressure and the heart rate of a young healthy adult for up to 5 hours [68, 74, 75]. Since the banning of ephedra in April 2004, sales of dietary supplements for weight-loss purposes have dramatically increased [76]. Some of the banned ephedra-containing products simply substituted the ephedra with *Citrus aurantium*. According to the Federal Trade Commission, *Citrus aurantium* is one of the five most popular ingredients that are found in over-the-counter (OTC) weight-loss products, as it claims to promote energy expenditure and suppress appetites [61]. Trials (see Table 6) conducted to investigate the efficacy of this ingredient have shown some positive results in the promotion of weight loss when compared to placebo groups [69, 77, 78]. However, these studies have had small sample sizes, used large doses, and no long-term study has taken place. In addition, it is hard to differentiate the effect of *Citrus aurantium* from other ingredients when these studies also included other herbal substances such as caffeine, St. John's Wort and Guarana. One published randomized, double-blind, placebo controlled trial

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[2] Or Adequate Intake (AI) when RDA is not available

using *Citrus aurantium* in weight-loss, at a dose far greater than present in Bioslim, found that subjects (n = 9) in the active ingredient group showed a significant weight loss of 1.4kg after 6 weeks, whereas the placebo group (n = 7) showed little or no changes [69]. All of the subjects received individualized instructions from a dietician to follow a 1800kcal/day American Heart Association Step One diet and to engage in a 3 day per week circuit training exercise programme with a physiologist. Other trials investigating the effect of *Citrus aurantium* have an even smaller sample size, and showed conflicting results [69, 77, 78, 79].

Table 6: Summary of four weight-loss trials that used *Citrus aurantium* as part of their anti-obesity treatment [61]

Study	Main ingredient (daily dose)	Study design	Duration	Result
Colker *et al.* [69]	975mg *Citrus aurantium* 528mg caffeine 900mg St John's Wort versus Placebo (with pill) and control (with no pill).	Blinded parallel groups. Randomized controlled trial. Active, N = 9 Placebo, N = 7 Control, N = 4 No dietary restriction.	6 weeks	Active group lost a significant amount of body weight (-1.4kg, $p < 0.05$) and placebo group did not (-1.1kg, $p < 0.1$). No adverse events were reported.
Jones *et al.* [77]	325mg *Citrus aurantium* (equates to 5mg of synephrine alkaloid) 125mg *Paullinia cupana* 5mg *Ginkgo biloba*	Open labelled. Week 1: 3800-4200 kJ/day diet, followed by week 2: using the supplement. N = 9	2 weeks	Week 1: an average weight loss of 0.94kg was found. Week 2: an average weight loss of 2.4kg ($P < 0.05$).
Kolman *et al.* [78]	Ephedrine and synephrine alkaloids (derived from *Citrus aurantium*), 5mg twice daily. versus placebo	Double blinded, randomized controlled, prospective trial. N = 30 All groups exercised and advised	8weeks	Significant weight loss found in the active group (-3.4kg) than the placebo group (-2.05). $p = 0.05$

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		22kcal/kg/day diet.		
Armstrong *et al.*[79]	85mg *Citrus aurantium* (5mg synephrine) 335mg Ma huang (20mg ephedrine) 40mg Pantothenic acid 910mg Guarana extract (200mg caffeine) 105mg Willow bark extract (15mg salicin) 50mg ginger root versus placebo	Randomized trial Active, N = 12 Placebo, N = 8 No dietary restriction.	44 days	Active group (-2.5kg) showed a significantly higher fat mass loss than placebo (-0.5kg). p = 0.033

These results suggest that *Citrus aurantium* in specific doses may have some benefit in enhancing weight loss when incorporating exercise and diet. However, none of these trials were rigorous or exceeded 6 weeks or used more than 20 subjects, consequently limiting the strength of these findings.

Although some of the *Citrus aurantium* trials reported significant weight loss compared to the baseline or the placebo group, the actual weight loss was less than both the stipulated criteria required by the FDA and the CPMP. This means that none of the products used in these trials can be considered to have a clinical benefit.

While the effectiveness of *Citrus aurantium* still needs to be confirmed, the adverse effects require some attention as several incidents of stroke, myocardial infarction and tachycardia have been reported [75]. Health Canada also reported 16 cases relating to the usage of *Citrus aurantium* where individuals experienced severe adverse effects such as tachycardia, ventricular fibrillation and cardiac arrest. The WHO subsequently issued an alert to health authorities regarding the use of this ingredient [80]. In South Africa, a young healthy bodybuilder who had no previous cardiovascular disease, consumed herbal supplements, including *Citrus aurantium*, to improve his performance and was reported to suffer from an acute myocardial infarction attack [81]. There may have been more adverse events, but the current surveillance system is poor and reports of such incidents are not compulsory.

Most unsubstantiated weight-loss products use polypharmacy (i.e. a combination of ingredients). Yet, actual clinical testing of the efficacy and safety of these combinations of ingredients has not taken place. Methylxanthines, such as caffeine, are found in various

plants such as Guarana and green tea [74, 82], which are both part of Bioslim's active ingredients. Caffeine stimulates the central nervous system and increases systolic blood pressure which may pose a danger to consumers with cardiac diseases. Individual ingredients on their own may not show any adverse effects, but the combined effect of them is not known. There is no evidence of whether or not these combinations have a synergistic or an antagonistic effect, which may result in enhanced toxicity.

The other Bioslim ingredients are not discussed here as they play a minor role, for they are used in miniscule amounts in comparison with the individual ingredients already mentioned.

Another well-known weight-loss product, Herbalife, also uses common herbal ingredients and is therefore often considered "natural" and safe by consumers. Herbalife has recently been associated with severe hepatotoxicity [83, 84]. In a recent study, cases of acute liver injury were reported in association with Herbalife usage [83]. In some cases, the damage was reversed when intake of Herbalife ceased. Another example of a potentially dangerous ingredient when taken in the wrong combination is St. John's Wort (*Hypericumperforatum*), which is toxic when ingested with medications such as antiretroviral drugs and may also cause photosensitivity [85]. Potential adverse effects for the most relevant ingredients are listed in Table 7.

Table 7: Adverse effects relating to specific ingredients

Ingredient name	Product Efficacy	Possible adverse events
Citrus aurantium	Inadequate clinical evidence to support efficacy [86].	At a high dosage (adverse events have been found after a single dose of 900mg of *Citrus aurantium*, which is an equivalent of 54mg of synephrine. In this study, participants are taking 200mg of *Citrus aurantium* per day.) Because of its stimulant effect, it may cause hypertension and cardiovascular toxicity such as: ischemic stroke, cardiac arrest, angina, myocardial infarction.
Gotu kola	Most studies use this in combination with other herbal ingredients. None show effective long term weight loss [87].	May cause nausea, gastrointestinal upset. There have been 3 reported cases of hepatoxicity associated with the intake of Gotu kola,

		dosage unknown.
Guarana	Little evidence for efficacy [86].	Adverse effects are related to the amount of caffeine content (Guarana contains caffeine). High dosages can cause gastric irritation, nausea, vomiting, restlessness, insomnia, tachycardia, tremors and chest pains.
Cascara sagrada	Little evidence for efficacy [71]	Mild gastrointestinal irritation. Long term intake may induce hypokalaemia, muscle weakness, cachexia and disturbed heart function (In this study, participants will be taking Bioslim for the period of one month only.)
L'carnitine	Little evidence for efficacy [71]	May cause gastrointestinal disturbances such as abdominal cramps, diarrhoea, nausea and vomiting. As well as heartburn, gastritis, body odour and seizures.
Pyruvate	Little evidence for efficacy [71]	May cause gastric distress.
Willow bark (salicylates)	Most studies use this in combination with other herbal ingredients. None show effective long-term weight loss [71].	May cause gastrointestinal irritation. In people who are allergic to aspirin, it can cause allergic reaction such as itching, as well as severe reactions such as anaphylaxis.

1.2.5 Adverse effects associated with usage of weight-loss drugs

Adverse events due to the ingestion of weight-loss drugs are difficult to monitor because of the lack of surveillance, authoritative regulation and registration of dietary supplements, as well as the vast number of products available in the market. Specific ingredients' adverse effects are also difficult to investigate in clinical trials, as most studies use a combination of herbal substances, and consequently it is difficult to relate specific side effects to one ingredient. In particular, if the adverse effects are rare, they are often undetected without a stringent surveillance structure.

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Palmer and colleagues carried out an observational study that included 21 poison control centres in the USA [88.] They found that 33% of the adverse events reported to the centre were related to dietary supplements. Of these events, 70% were regarded as mild (with minimal consequences and short term effects), 24% as moderate (systematic, e.g. an isolated seizure or arrhythmia with hypertension), 6% severe (life-threatening e.g. respiration compromised and requiring intubation) and 1% resulted in death [89]. Similar findings were reported in other studies [90, 91]. It was further found that most of these events were associated with herbal substances such as Ma huang (*Ephedra sinica*) (thought to be responsible for the toxicity of Herbalife), Guarana, ginseng (*Panax*genus) and St John's Wort.

Moreover, negative events were found to be significantly more frequent in individuals ingesting multiple ingredients, rather than single ingredients. Most OTC weight-loss products on the market use polypharmacy (with no proof of synergistic, antagonistic or other types of interactions). In fact, they often advertise this fact to promote the efficacy of the product, claiming that the potency of the drug is now strengthened and yet the side effects have been reduced as a result of the use of polypharmacy. Dietary supplements similarly lack the endorsement of clinical studies to ensure the safety of long-term ingestion. Persistent supplement usage may lead to the build-up of chemicals and increase the toxicity in tissues [92].

A review by Lenz and Hamilton [72] reported that 80% of overweight or obese individuals do not seek medical professional help for their first attempt at weight-loss. This is of concern, as hypertension is often found in overweight and obese individuals and some dietary supplements such as caffeine, *Citrus aurantium a*nd Guarana have been shown to raise blood pressure and hence contra-indicate the usage of such substances [93]. Most individuals assume that these herbal substances are natural and harmless, and are therefore unlikely to report the usage of a dietary supplement to their doctors (which may compound potential side effects of drugs already being taken for other pre-existing conditions). In fact, their use may be a hidden practice [94]. Lack of help from medical professionals may hinder individuals from receiving scientifically sound information on healthy weight-loss methods, further exacerbating the problem of obesity. Findings from NHANES III suggested that individuals might start using OTC weight-loss drugs in place of lifestyle changes [95].

Other adverse events frequently associated with dietary supplement use are myocardial infarction, coagulation disorders, anaphylaxis and hepatic disease [89]. A further concern is that consumers report frequent usage of herbal substances to treat diseases and use them as prescribed drugs, which is not the intended indication. There seems to be confusion over the difference between prescription products and dietary supplements, which reinforces the need

for government regulation, particularly as the manufacturers may promote the dietary supplement as a highly effective equivalent to prescription medication, but even better, because it is safe and made from natural ingredients.

1.3. Regulation of weight-loss drugs and dietary supplements

All prescription weight-loss drugs, such as Orlistat, are currently regulated by the Medicines Control Council (MCC) under the Medicines and Related Substances Control Act (MRA) (Act 101 of 1965) [96].This act regulates the manufacturing, distribution, sale, and marketing of medicines to ensure that they are safe and effective for consumers as indicated by scientifically sound clinical trials.

However, all nutritional supplements, specifically ones marketed to aid weight-loss, may not be considered as medicine, but as complementary medicine. This means that there is no requirement for clinical trials before they appear in the market. Hence the efficacy, safety, product quality and accuracy of claims are not tested nor controlled. Furthermore, the actual regulation around complementary medicine is still a perplexing issue. According to the Principal Medicines Regulatory Officer of MCC [97], a government gazette has been issued in 2002, acting as a call-up notice for all the products that are available in the market and refer to themselves as complementary medicines in terms of the Medicines and Related Substance Control Act, 1965.

According to the Act, medicine is defined as

any substance or mixtures of substances used or purporting to be suitable for use of manufacture or sold for the use in:

a) diagnosis, treatment, mitigation, modification, or prevention of a disease, or abnormal physical or mental state, or the symptoms thereof in man, or

b) restoring, correcting, or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine.

All medicines for human use are subject to this law, including complementary and complementary biological medicines.

This call-up process would assist with the auditing of all products not only for registration purposes, but so that MCC could review their claims of safety, quality and efficacy, with the aim of determining if these product pose a public hazard or not. However, this auditing process was never promulgated.

To further complicate the issue, a call-up process seems unnecessary if according to section 14 of the Medicine and Related Substances control Act there is:

14. Prohibition on the sale of medicines, which are subject to registration and are not registered.

In October 2009, the MCC was about to rescind the 2002 "call-up" in order to prevent further misunderstanding and abuse of this flawed process, but was threatened with legal action by the "complementary" medicine industry and it was therefore not followed through [67].

In comparison, the USA's medicine regulatory body, the FDA (Food and Drug Administration) defines a dietary supplement as a product that is taken by mouth and contains 'dietary ingredients' intended to supplement the diet. The 'dietary ingredients' in these products include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites [59].

These dietary ingredients are regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994, which is meant to provide consumers with easy access to dietary supplements without a prescription and to allow manufacturers to push products onto the market without following the regulations of the Federal Food, Drug and Cosmetic Act (for drugs) and consequently no requirements for carrying out clinical trials to test their efficacy and safety. According to the act, all dietary ingredients that were marketed before 1994 are considered to be safe, and all new ingredients that are introduced after this date will require the submission of a pre-marketing notification to the FDA to review the information that is submitted by the manufacturers, such as published journal articles. Otherwise, it is the manufacturer's responsibility to ensure that the product is safe and that the labelling is truthful. In addition the act relies heavily on the public and the manufacturer themselves to voluntarily report any adverse events or defective products [98]. Although the USA may have clearer defined regulations for complementary medicine, the availability of products with unlawful and unsubstantiated claims for weight-loss are still commonly found there. As Americans are some of the highest spending consumers of diet programmes and related products, at an estimated amount of 30 billion dollars a year, it is hard to keep up with all the products and manufactures still finding ways to enter the market under the registration of dietary supplements and not as medicines. According to the Federal Food, Drug, and Cosmetic (FD&C) Act, under the labelling section, if the labelling includes:

a claim relating to an effect on the structure or function of the body, a claim of general well-being, or a claim of a benefit related to a classical nutrient deficiency

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disease, the product must bear a disclaimer stating that FDA has not evaluated the claim and that the product is not intended to diagnose, treat, cure or prevent any disease.

This act is an attempt to discourage manufacturers from registering products under dietary supplements in order to avoid stringent clinical trials, but still claiming the effect of a registered medicine. However the USA Federal Trade Commission (FTC), which is responsible for the monitoring of the advertising and marketing of products, does not always reinforce the Act stringently and some dietary supplements that violate the Act can still be found in the market. An example of the FTC charging a diet pill company for deceptive advertising and corrupt practices is that of Sistema Silueta. The advertiser of this cellulite reduction product made false claims that this product could break down cellulite and fat when the cream was applied to the body. It further stated that the treatment would penetrate the skin and dissolve the fat cells to reduce cellulite in the buttocks, and that the body would then excrete them. The FTC has been able to successfully refute such claims, and in order to protect the consumers, has prohibited the company from manufacturing any cosmetic or drug in the future that would transgress the act.

In South Africa, the MCC sets the rules and the regulations like the FDA, but the MRA enforces such legislation. The MCC has been revising regulations relating to medicines, and it is believed that it contains a section governing so-called "Complementary medicines". However, while the MCC is finalising the complementary medicine regulations and registration procedures, manufacturers of dietary supplements are not without any restraints. Other regulatory bodies such as ASA (Advertising Standards Authority of South Africa) have also laid out a Code of Advertising Practice for the complementary medicine industry to adhere to [99]. ASA is an independent body set up by the marketing communication industry to self-regulate advertisements in the general consumers' interest.

This code is based on the International Code of Advertising Practice, prepared by the International Chamber of Commerce. According to the ASA code these are some of the unacceptable claims:

"Product X is safe"

"Contains no harmful substitutes with side effects"

And/Or

Claims implying that this product is a medicine i.e. interfering with the normal physiology of the body, e.g.

"Product X increases/speeds up metabolism"

"Product X melts fat away"

"Product C makes fat cells shrink"

"Product X contains bio-active ingredients"

And/Or

Claims that quantify mass loss:

If the expected mass loss is quantified for a product, the amount stated shall not exceed 1kg per week, as this is the accepted level for safe mass loss. Furthermore claims such as "Helps you slim fast" and "Easy weight loss" etc. are not permissible.

Despite the clearly stated advertising guidelines, such claims can still be found often on TV, product packaging and in magazines.

The Federal Trade Commission found that weight-loss advertising is mostly full of misleading claims, since 40% of the adverts make at least one claim that is almost certainly false, and 55% make at least one that is likely to be false. Nearly 50% of the adverts that were included in the survey promised weight loss without dieting or exercise [100].

Other popular marketing gimmicks that are often found in adverts are testimonials. Although these are not prohibited by the ASA code, it requires that the testimonials be genuine and substantiated. All photographs should be dated and signed by the person in the included photo [99]. However, it is questionable whether the individual's weight loss in the testimonial is due to the actual product being marketed or other interventions such as a very low caloric diet and intensive exercise.

The ASA code provides a good basis for ethical advertising, but there is no formal surveillance body for illegitimate adverts and ASA relies on the general public, specifically health professionals, to report any violation of their codes to ensure that all of the manufacturers' marketing is compliant.

1.4. Negative impact of perpetual dieting attempts

The vast number of weight-loss products is overwhelming for the consumers; nevertheless the market is constantly expanding with new products, each with a persuasive infomercial guaranteeing weight loss. Most of these weight-loss drugs have no effect at all; some result in temporary weight-loss in some individuals. Whatever the case, as in an energy-restricted diet, the weight that was lost is generally regained when the diet or drug therapy ceases, or there is regression to the mean, leading to weight cycling.

"Weight cycling" can be defined as fluctuation in weight, specifically led by a series of unsuccessful dieting attempts in which the subject regains the weight that was previously lost. Some studies speculate that obese and overweight people might have a down-regulation of resting metabolism post weight-loss, causing them to be obesity prone, and that chronic dieters may have a lower-than-normal resting energy expenditure [101]. These speculations are not supported by most studies; what is certain, however, is that frequent fluctuation of weight has a negative impact on health.

A Women's Ischemia Syndrome Evaluation (WISE) study found that there was an association between high-density lipoprotein cholesterol (HDL-C) and weight cyclers. HDL-C was on average 7% lower in weight cyclers than non-cyclers. This effect is dose dependent, as women who had lost 22.7kg in each cycle had 21% less HDL-C compared to their counterparts [102]. The Framingham study further validates this by showing a positive association between weight variations and an increased risk of coronary heart disease [103].

From the psychological point of view, perpetual unsuccessful attempts at weight loss may have a negative impact on one's self-esteem, resulting from the negative connotations associated with being overweight or obese [104]. Various studies have shown that the media often stereotype overweight individuals as unattractive, unsuccessful and socially inept [60]. Furthermore most dieting pills guarantee weight loss or decrease in fat mass, backed by claims such as a "30-day payback guarantee", and some implicitly suggest that a result can be achieved with unrestricted eating and in the absence of exercise. As a result, consumers are led to believe that the pill is the key to success, so that if weight loss is not achieved then the fault must lie with them. Meanwhile, the pill itself may not have had any effect to begin with. Thus, one can see how weight-loss drugs may not only have dangerous clinical side effects, but can also negatively influence consumers psychologically by exacerbating low self-esteem and related psychological issues. They can also delay individuals from seeking professional help which may impact on their health, e.g. type 2 diabetes or hypertension can become uncontrolled or irreversible unless there is an intervention early on.

1.5. Placebo effect

As in most clinical trials, a placebo group is included in this randomised control study to ensure that any effect observed in the active-pill group is not due to the placebo effect, which is defined as the therapeutic effect of an inert drug and used to validate drug effectiveness [105, 106]. As the effect of a drug that is measured from an interventional trial, is the result of various elements and not only the outcome of the pharmacological effect, factors such as regression to the mean (including the number of subjects, trial duration, design of the study and the end measure of responses), natural remission of the disease and placebo response (due to the administration of the drug) also have an impact on the effect measured [107]. The placebo group is therefore used to control these other factors. For a drug to be proven to be effective, the outcome measure should be significantly greater in the treatment group than in the placebo group.

It is difficult to predict and measure the actual placebo effect, as different outcome measures, disease profile and the history of the disease can influence the response rate. Nonetheless, it is commonly thought that 30% of the subjects in the placebo control group experience placebo effects. According to Beecher's result [108], a wide range of response rates, varying from 7% to 49% have been observed in various studies [109]. Hrobjartsson and Gotzshe carried out a meta-analysis study in 114 trials relating to the placebo effect and found that a significant difference between the placebo group (that receives treatment with no effect) and a non-treatment group (group that receives no treatment at all) is only observed when the outcome measure is something self-reported and subjective, e.g. pain. Hence, an outcome measure that requires objective reports, e.g. observation of blood pressure or asthma, may have a much lower placebo response rate compared to subjects' reports of pain [109].

One of the possible mechanisms for placebo effect may be explained by classical conditioning. The act of taking a drug can be regarded as a conditioned stimulus, due to its visual, tactile and gustatory effect on the individual. Repeated measures of this act can be paired with the unconditioned response. For example, whenever one takes a painkiller it resolves the pain of a headache. When the pill is switched to an inert drug, the conditioned stimulus, the act of taking the drug, can still elicit an unconditioned response, resolving of the pain [110], as the stimuli triggered by the placebo can activate the release of various neurotransmitters and modulators that bind to the same receptor to which the actual chemical of the drug would bind - thus prompting the same pharmacological effect [107]. But can the same effect be experienced when taking a weight-loss drug?

The placebo effect is believed to be modulated heavily by the role of expectancy, which is defined as the individual's expectation regarding the progress of the disease and is directly related to the individual's belief in the efficacy of the administered drug [111]. As illustrated in the sports field, the mind has a great impact on performance; study results have shown that, performance can be greatly improved by prescribing placebo pills without actual ergogenic effect, depending on the athlete's belief in the efficacy of the substance [112].

Similarly, the power of advertising can also play on the individual's mind and encourages individuals to expect highly effective drugs for weight loss. The placebo effect is then enhanced when subjects believe in the effectiveness of the pill, as suggested by convincingly authoritative sources such as the media or testimonials. Studies have shown that, even though the placebo effect is due to psychological belief, it can evoke physiological reactions. This is illustrated by studies from Columbia and Michigan universities [113], in which volunteers took an inert substance and believed that they had been given a potent painkiller. It was observed that some of these volunteers released opioids (the body's natural physiological pain-relief mechanism) and the pain was subsequently relieved. See Table 8 for a list of other physiological reactions that can be triggered by the placebo effect. Thus, when consumers trust the effectiveness of an ineffective weight-loss drug, it may result in them losing weight as a result of subconscious psychological responses (for example, potential hormone changes that promote metabolism, or the subject making conscious or unconscious modifications to diet or exercise).

Table 8: Possible physiological responses that are elicited when a placebo is administered [107]

Disease / system for the targeted drug effect	Possible mechanism or physiological response to placebo treatment
Pain	Release of endogenous opioids and cholecystokinin.
Parkinson's disease	Dopamine released in the striatum changes the firing pattern of sub thalamic nucleus neurons.
Depression	Brain metabolism changes and possibly inhibits serotonin reuptake.
Cardiovascular system	Reduction of β-adrenergic activity of the heart.

Immune system	Immune mediators such as lymphocytes can be preconditioned by actual immunosuppressive drugs.
Endocrine System	Hormones such as the growth hormone are preconditioned.

As part of the marketing scheme, attractive packaging can also influence subjects' expectancy, which was illustrated by Kienle and Kiene *et al.* [114]. Packaging, colour and size of the pill have an impact on the individual's perception of the drug. For example, red is believed to be more stimulating and pale colours, in contrast, to be more relaxing. In addition, conditioning can also have an effect, as individuals can associate various therapeutic procedures and ways in which drugs were administered (intravenously or by ingestion) from their past and then pair the experience with successful treatment of a disease. Thus, an individual may pair an intravenous injection to a more successful treatment result or the effectiveness of the drug may be more convincing when three pills (as found in the Bioslim Once a Day package) are prescribed than one [115]. In this study the placebo group is not only included for the validation of the drug's effectiveness, but also to investigate whether aggressive marketing schemes such as persuasive TV adverts, appealing packaging and testimonials further add to the power of the placebo effect and how this group compares to groups receiving placebo pills in "no name" packaging.

Wansink [116] has reported that an individual may unconsciously make or consider over two hundred food-based decisions a day, and therefore any factor that makes any of these thoughts conscious, may result in the individual altering that "food script" and may result in a change in that individual's behaviour towards food, e.g., to eat less. Therefore an individual taking an inert substance may still lose weight as a result of becoming conscious of food intake [116].

1.6. Anthropometry

1.6.1 Weight measurement and BMI

One of the most commonly used nutritional assessments is weight measurement. It is either recorded as part of weight history to observe any fluctuation or combined with the individual's height measurement, in order to work out the body mass index (BMI). This is also known as Quetelet's Index and is calculated by taking the weight (kg) of the individual

divided by the square of his/her height (m) and is used because weight on its own provides little anthropometric information about the individual. This measurement is recommended by the National Research Council's Committee on Diet and Health [117] as a tool to assess overweight or underweight individuals. It is also commonly used in National surveys, such as the NHANES [26] from the USA and National Food Consumption Survey [7] in South Africa. BMI is easy and practical to use in the clinical setting and its classification has been developed by the Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults and endorsed by WHO [4]. Table 9 shows the BMI classification cut-off points for the various degrees of overweight, which are identified by the association found between mortality risk and BMI[2]. It has also been shown to predict total adipose tissue with an error of 10% or less when compared to CT results. Although it may be a good indicator for excess fat mass, it does not take age, gender or individuals with extreme body composition into account. For example, BMI maybe overestimated in very muscular individuals such as body builders or underestimated in the elderly with loss of lean mass [117].

To improve the usefulness of BMI in body fat mass prediction, the WHO has recommended the inclusion of waist circumference when carrying out nutritional assessments. Hence BMI and waist circumference can classify individuals for overweight and abdominal fatness respectively[1]. Furthermore, as indicated in Table 9 waist circumference and BMI are able to estimate mortality risk.

Table 9: Classification of obesity and associated health risk with waist circumference [64]

	BMI (kg/m^2)	Obesity Class	Disease Risk according to BMI and waist circumference	
			Men ≤ 102cm Women ≤ 88cm	Men > 102cm Women > 88 cm
Underweight	< 18.5		-	-
Normal	18.5 – 24.9		-	-
Overweight	25.0 – 29.9		Increased	High
Obesity	30.0 – 34.9	I	High	Very high
	35.0 – 39.9	II	Very High	Very high
Extreme Obesity	≥ 40	III	Extremely high	Extremely high

1.6.2 Skin-fold measurement

Obesity is defined as an accumulation of excess fat. In order to monitor the progress of treatment for overweight and obesity, the skin-fold assessment tool is used in measuring body composition, specifically changes in total fat mass. Various other methods and pieces of equipment have been developed to analyse body composition, such as under water weighing (UWW) and dual-energy X-ray absorptiometry (DXA), which are regarded as valid and reliable reference methods. However, such equipment is often not available due to cost and lack of trained operators [118].

For a more portable and accessible method, anthropometric techniques may be considered. One of these techniques is the measurement of skin-fold-thickness with a calliper at various sites on the body. The calliper is used to measure the subcutaneous fat. The operator then estimates the total body fat by converting these measurements, using various prediction equations for specific population groups [119]. Besides being an easily accessible tool, skin-fold measurement is also a non-invasive, painless and cost-effective method of estimating body fat mass. Researchers can easily be trained to correctly operate the calliper, and in addition to test the inter- and intra-rater reliability to ensure accuracy. The skin-fold measurement method was adopted in the NHANES as one of the tools to assess overweight and obesity [120].

Accuracy of skin-fold measurement depends heavily on the appropriate choice of a prediction equation, as different subject groups have varying fat-free mass density, dependent on age and sex. For example, women have a lower fat-free mass density than men. Therefore, fat mass is often overestimated when the value for fat-free mass density is assumed to be the same as for men. Durnin and Womersky attempted to overcome this problem by developing a series of prediction equations that are age- and sex-specific and can also be used in general population groups [121]. Durnin and Womersky's prediction equations were further supported by Andrade *et al*. [122], who tested them against a reference method, namely magnetic resonance imagining (MRI). The results from the MRI and the skin-fold measurement were found to be in good agreement. A study by McNeil *et al*. [123] indicated that skin-fold measurement has an accuracy comparable to other techniques such as bioelectric impedance analysis (BIA) and body-water dilution in lean and overweight women. Skin-fold measurement has been shown to have the ability to measure fat mass and fat-free mass within an accuracy of 3-4% [124].

A drawback of skin-fold measurement is that it is difficult to estimate all sources of error, as these may vary depending on the make of calliper and the operator taking the measurements. Ideally it is recommended that one calliper be used throughout the study. In addition, the technique is not recommended for use on subjects who have a BMI in excess of 40, as the

skin-fold thickness may be greater than the width of the calliper, making it impossible to take accurate measurements.

1.6.3 Waist-circumference measurement

The BMI is commonly used for classification of overweight and obesity in men and women. However, it does not have the capacity to determine body-fat mass and its distribution. This is significant, as body-fat distribution is found to be a powerful predictor for cardiovascular and other disease risk factors [125]. In particular, increased visceral and abdominal adipose tissue has been shown to strongly correlate with metabolic and cardiovascular diseases. Waist circumference alone has been shown to be more useful and closely associated to central obesity than BMI or waist-to-hip ratio [126]. A study by Booth *et al.* [127], indicated that even self-reported waist circumference is useful in assessing and monitoring overweight and obesity in clinical studies.

A guideline for management of obesity developed by the National Institute of Health (NIH) has also recommended the use of waist circumference and BMI as reliable and easily available tools for identifying obesity and monitoring treatments [122]. Waist-circumference is a simple metric to measure as it only requires a measuring tape. Additionally, the measurement error has been found to be relatively low compared to other anthropometric methods. However, it is not recommended for obese individuals with a BMI > 45, as the abdominal fat would be too large for accurate measurements. Height and BMI can be used as alternative means of fat prediction for these individuals [128].

1.7. Statement of research question

Overweight and obesity is a serious and growing global epidemic problem. It significantly increases the risk of various diseases such as cardiovascular, diabetes and a number of cancers. Successful weight-loss treatment requires long-term lifestyle changes with the aid of professional health workers to provide sound clinical advice. This proves to be challenging for various individuals and additional aid is often required to assist with the weight-loss process. There are numerous prescription weight-loss drugs that are currently approved by FDA for their effectiveness and safety, such as Orlistat and Sibutramine. Usage of such drugs should be long-term and often weight is regained when the drug is discontinued. Even then, their effectiveness is generally marginal. In addition to the challenges of weight loss, medical help is seldom sought by the general public, as overweight and obesity is not typically regarded as a disease, but is rather associated with sloth and lack of self-control. Consequently, the popularity of over-the-counter weight-loss supplements has escalated, as they are often advertised as quick-fixes and with a 100% success rate without consumers

changing their lifestyle. Aggressive marketing schemes often include convincing testimonials and skilful packaging, which may also have an impact on the placebo response. The power of advertising can play on consumers' minds and a placebo effect can be evoked when subjects believe in the effectiveness of the drug as suggested by authoritative figures such as the media or by testimonials.

These supplements form a multi-million rand market which is continually expanding as there are no regulations in place in South Africa to restrict manufacturers. Manufacturers are also not required to conduct methodologically sound efficacy studies before they make the supplements available to the consumers.

The author has no knowledge of previous studies that have been carried out to verify the effectiveness and the possible side effects of an over-the-counter weight-loss supplement in South Africa, and in particular the influence of advertising and branding on the placebo response. In this study we have chosen Bioslim, as it is one of the dominant brands in the dietary supplement market, specifically for weight loss. The findings of this study will provide some insight into the accuracy of claims made by Bioslim and to record any adverse side effects. In addition the results extend current understanding of the impact of intensive marketing on placebo effects. This study can also form the basis for a larger study which could include a variety of non-prescription products on the market, thus assisting consumers in making a better choice when purchasing a dietary supplement product. Lastly, the study may create awareness on the usage of dietary supplements in this country and improve vigilance over unsubstantiated products.

Chapter 2
Methodology

2.1 Aim

To investigate whether Bioslim results in greater weight-loss than a placebo, and whether the marketing of the Bioslim brand has an influence on the placebo response.

2.2 Objectives

1. To evaluate whether there is a significant difference in weight reduction, according to Bioslim Once a Day claim, when comparing the active and the placebo groups over a period of one month.
2. To assess whether Bioslim shows a significantly superior effect in reduction of fat mass and waist circumference when compared to a placebo, and when other anthropometric means are used to determine the efficiency of Bioslim as a weight-loss drug.
3. To investigate if subjects follow the guideline, "Only effective when used in conjunction with a kilojoule-controlled diet and moderate exercise."
4. To document any self-reported side effects of the product.

2.3 Study Design

This study was an experimental, randomised, double-blind placebo-controlled prospective intervention trial.

2.3.1 Subjects

Study population

The study population was comprised of overweight adults in the Western Cape area.

Sampling techniques

All shopping centres that sell Bioslim in the Western Cape area had been considered. Kenilworth Centre and Century City were the final two shopping centres that were selected, based on the wide range of consumers that they attract and the permission obtained from the various centres to carry out the study. The socioeconomic status of the patrons that visited these two sites varies from high to low, as consumers from various suburbs visit these two shopping centres. In each shopping centre, a stand was set up on various occasions to hand out fliers, attached in appendix 1, and to sign up keen participants.

Advertisements (refer to appendix 1) were also placed in the local community newspaper in September and October 2008 inviting volunteers to join the study. These newspapers cover areas that surround the two shopping centres. Advertisements were placed in *Tygertalk* and *Tabletalk* to be distributed in the Goodwood, Parow, Thornton, Milnerton and Tableview

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area; as well as in *The Tatler* – serving the Southern suburbs - to cover areas such as Mowbray, Observatory, Pinelands, Rondebosch, Newlands, Claremont and Kenilworth.

All efforts were made to ensure that the implementation of the study mimicked, as closely as possible, the manner in which consumers would normally make use of the product. Therefore, the study was conducted inside the shopping centres, away from a hospital or academic setting in order to minimise external factors that might have influenced the placebo response.

Subjects who were interested in participating in the study were asked to contact the investigator telephonically and to leave their details with the research assistant. The investigator then checked the eligibility of the subject. If he/she qualified, arrangements were then made to meet the subject in person at the office inside the relevant shopping centre.

2.3.2 Inclusion and exclusion criteria

The study's inclusion criteria were:

- Subject is older than 18 years.
- Subject has a BMI > 25.
- Subject had heard of Bioslim before joining the study.
- Subject had given consent by signing the informed consent form (see Appendix 2).

The study's exclusion criteria were:

- Subject is receiving treatment for heart condition.
- Subject is receiving treatment for diabetes mellitus.
- Subject is pregnant or breastfeeding.
- Subject has taken Bioslim before.
- Subject has a BMI > 40.

2.4 Methodology

2.4.1 Preparation of placebo and packaging

Solaltech, a pharmaceutical company, produced the placebo pill which resembled the real Bioslim pill in appearance. Information, such as "Only effective when used in conjunction with a kilojoule-controlled diet and moderate exercise", which appears on the actual Bioslim packaging, was also on the No Name packaging, which was stripped of any reference to the branded product.

The research assistant packaged the pills, placing placebos in either Bioslim or No name packages, and active pills in either Bioslim or No Name packages. This resulted in four groups of pills. The groups were then colour coded and a subject identification number (ID) was randomly assigned to each of the four colours. At the baseline meeting, the investigator handed out one of the four formulations to each participating subject according to their subject ID, which was based on the order of the subjects' enrolment. Each subject had an equal chance of being placed in any one of the four groups. This process occurred without the investigator, or the subjects' knowledge of the content of the formulation.

The study subjects were randomised into one of the following four groups:

Group Red (Placebo branded group)

The placebo in the Bioslim packaging.

Group Green (Placebo brandless group)

The placebo in the No Name packaging.

Group Yellow (Active branded group)

The Bioslim formulation in Bioslim packaging.

Group Orange (Active brandless group)

The Bioslim formulation in the No Name packaging.

Table 10: Study groupings

Packaging	Formulation	
	Active Bioslim pill	Inert placebo pill
Branded packaging	Group Yellow	Group Red
Brandless packaging	Group Orange	Group Green

Groups Green and Orange (brandless packaging) had a menu planner and instructions included inside, which simulated the ones found in actual Bioslim packaging. Groups Yellow and Red received the actual Bioslim package inserts.

The original Bioslim packaging contained 3 bottles with 3 different preparations of the active Bioslim pills inside, as well as a meal planner. The same were also found inside the placebo packaging, i.e. 3 plain white, similarly sized containers without the Bioslim label and a meal planner without any Bioslim logo. The same number of pills was also placed in each bottle to ensure that all subjects would take 3 pills for the first 7 days and 2 pills for the next 21 days during the trial period.

The products were given to subjects individually according to the randomisation sheet, assigning them to one of the four groups listed above. They were instructed to behave towards the product as if they had bought it from the shop themselves. No further instructions were given, including dietary instructions and menu planners.

2.4.2 Anthropometric measurements

The following measurements were carried out at the baseline and at the follow-up meetings according to literature [129], and were conducted in an office space inside each of the shopping centres. All measurements were repeated three times and the average of the three was used for data analysis.

2.4.2.1 Weight (to the nearest 0.1 kg)

The subjects were asked to stand still in the middle of the scale without touching anything and their body weight equally distributed on both feet. The weight measurement was read to the nearest 100g and recorded. The subjects were requested to empty their pockets and remove any heavy jewellery, jackets and shoes before standing on the electronic scale. The scale was calibrated each day. Height (to the nearest 0.1cm)

A stadiometer was used to measure the height of subjects. They stood barefoot, with their heads in the Frankfort horizontal plane and closely against the stadiometer, their arms resting on either side. The subjects inhaled deeply just before each measurement was taken. At each repeated measurement, subjects were asked to stand away from the stadiometer, to repeat the alignments.

2.4.2.2 Waist circumference (to the nearest 0.1cm)

A Hoechstmass 150cm tape measure was used to measure the waist circumference. Subjects were asked to stand upright, without clothing and the measurement was taken at the smallest circumference between the lower rib cage and the upper hipbone. The tape was tightly wrapped around the waist, without compressing the skin and parallel to the floor. Each measurement was taken after the end of a normal expiration.

2.4.2.3 Mid upper arm circumference (to the nearest 0.1cm)

The mid upper arm circumference was measured with a two metre anatomical measuring tape by locating the midpoint between the scapula and the tip of the elbow. The arm was relaxed and resting on the side of the body. The tape was firmly wrapped around the midpoint and parallel to the floor.

2.4.2.4 Skinfold thickness measurements (to the nearest 1mm)

The triceps, biceps, supra-iliac and subscapular skinfolds were all measured using the FatTrack2 electronic calliper. The accuracy of the equipment was ensured by zero calibration before each measurement. Subjects were asked to undress and to have only their undergarments on. At each site, the thumb and the index finger pinched the subjects one centimetre above the actual site and the calliper measured the midpoint of the skinfold, without over compressing the skinfold. All measurements were taken on the right half of the body.

2.5 Questionnaire

At the follow-up session, which was one month after the baseline assessment, a questionnaire (see appendix 3) was administered. The questionnaire was compiled by the investigator, the study supervisor and co-supervisor. The questionnaire was compiled to investigate subjects' previous experience with other over-the-counter weight-loss drugs, and specifically their views on the drugs' efficacy and if there were any adverse side effects involved. Similar questions were asked regarding their experience with Bioslim during the study period. Lastly, questions regarding an energy restricted diet and exercise, that were or were not undertaken by the subjects during the study period, were also included. Measurement of the physical activity level was based on the subjects' self-reports, as one of the study objectives was to investigate whether the subjects did or did not change their physical activity levels and whether they attempt lifestyle modification during the study period.

Subjects were asked to complete the questionnaire by themselves and to ask for assistance from the investigator if they were unsure of any question. These were then coded and entered by both the investigator and a research assistant to ensure inter-reliability.

2.6 Data and Statistical Analysis

All data were entered into a Microsoft Excel spread sheet, where the statistician provided assistance with the analysis of the data. The computer program, STATISTICS 8.0, was used to carry out analysis of the data.

For ordinal and continuous data, histograms and frequency tables were used to describe the data. For continuous data, two-way repeated measures ANOVA were used to analyse the data to find associations within the four groups. For nominal data, the maximum likelihood chi-square statistic was used for analysis. A significance level of 5% was used.

2.6.1 Body mass index (BMI)

This was calculated by taking the weight in kilograms divided by the height squared in metres.

2.6.2 Estimation of body fat mass from skinfold measurements

Body fat mass was calculated by following Durnin and Womersley's skinfold prediction equation that made use of the sum of four skinfold measurements. Subjects' gender and age were taken into consideration when calculating the body density (Table 11).

Body fat mass is then calculated as follows:

Fat mass (kg) = body weight (kg) x [(4.95/D) – 4.5]

Fat mass % = Fat Mass (kg) / body weight (kg) x 100

Table 11: Equations for determining body density. The four skinfold types are biceps, triceps, subscapular and supra-iliac (measured in millimetres) [121].

Age (years)	Men	Women
17-19	1.1620-0.0630 x (log Σ4 skinfold sites)	1.1549-0.0678 x (log Σ4 skinfold sites)
20-29	1.1631-0.0632 x (log Σ4 skinfold sites)	1.1599-0.0717 x (log Σ4 skinfold sites)
30-39	1.1422-0.0544 x (log Σ4 skinfold sites)	1.1423-0.0632 x (log Σ4 skinfold sites)
40-49	1.1620-0.0700 x (log Σ4 skinfold sites)	1.1333-0.0612 x (log Σ4 skinfold sites)
50+	1.1715-0.0779 x (log Σ4 skinfold sites)	1.1339-0.0645 x (log Σ4 skinfold sites)

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2.7 Ethics and Consent

Ethics approval was obtained from the University of Stellenbosch Ethics Committee before the research project was conducted. An English Participant Information and Consent form (refer to appendix 2) was given to all subjects before enrolled into the study. Consent forms in other languages were not required, because all participants spoke English.

All participants entered the study having signed the consent form after the investigator had given them a comprehensive oral and written explanation of the study and they were informed that participation in the study was entirely voluntary and they were free to decline to participate. Declining to participate would not affect participants negatively in any way whatsoever. It was the subject's right to withdraw from the study at any time without providing a reason. Any subject that did not follow the study protocol will be removed from the study. The information that would be collected would be treated as confidential information; if the results were to be published all identities of the participants would remain anonymous.

Chapter 3

Results

3.1 Demographic Information

In total, 110 subjects were recruited for the study. However, data was only available for 87 subjects, as 23 did not complete the study. The drop-out group consisted of 23 participants, of whom 8 had been randomised to receive the active drug and 15 to receive the placebo. Drop-out reasons were: unable to attend the follow-up session (12 subjects); did not complete the full course of the product (10 subjects); and one subject who was on the active drug, who stopped using it after reporting severe headaches.

The mean age for the final study group was 40.49 (standard deviation, SD ± 10.05 years) and is predominantly white (53%) and female (90%). Table 12 describes the demographic characteristics of the study population.

Table 12: Demographic characteristics of the study population

Subject Characteristics	Female N = 78 (90%)	Male N = 9 (10%)	Total Subject N=87
AGE			
18 TO 29 YEARS	9	3	11 (13%)
30 TO 39 YEARS	28	1	29 (33%)
40 TO 49 YEARS	25	2	27 (31%)
50 TO 59 YEARS	15	2	17 (21%)
60 +	1	1	2 (2%)
Ethnicity			
White	40	6	46 (53%)
Black	7	0	7 (8%)
Coloured	30	3	25 (38%)
Indian	1	0	1 (1%)
4 study groups			
Yellow (Active drug with Bioslim packaging)	21	5	26 (30%)
Orange (Active drug with No Name packaging)	20	2	22 (25%)
Green (Placebo with No Name packaging)	21	1	22 (25%)
Red (Placebo with Bioslim packaging)	16	1	17 (20%)

3.2 Anthropometry

3.2.1 Total study group (n = 87)

The baseline and follow-up anthropometric characters for the total study population are shown in Table 13. The mean BMI for the population at baseline was 31.90 kg/m^2 with male mean BMI = 32.38 kg/m^2 and female mean BMI = 31.84 kg/m^2. Both are classified as class I obesity. Fat mass percentage means at baseline for the male group were 28% and 38% for the female group. These are considerably greater than the recommended levels (25% for male and 35% for female) and are considered as obese, based on the relationship between BMI and fat mass percentage reported by WHO [130] (there is no exact cut off percentage available for body fat mass percentage derived from direct measures).

The same was found for the mean waist circumference at baseline, where the male group had a mean of 108.21cm and the female, 99.28cm, both groups exceeding their individual gender categories' recommendation of 102cm for men and 88cm for women according to the Practical Guide by the National Institute of Health (NIH) [104].

At the follow-up measurement, none of the measured anthropometric variables had changed significantly compared to the baseline for the total population.

None of the anthropometric measures had any significant changes amongst the female subjects when comparing baseline to follow-up measurements. The same was true of the male subjects apart from the fat mass percentage which had a significant change ($p = 0.03$).

The repeated measures analysis of variance test showed that in this study, that males and females behave differently from baseline to follow-up ($p = 0.02$): females had a marginal weight-loss of 0.014 kg, whereas males gained 1.03 kg.

There was no significant difference in anthropometric characteristics such as BMI ($p = 0.48$), waist circumference ($p = 0.89$) and fat mass percentage ($p = 0.43$) at baseline between the four study groups. Any changes between groups at follow-up could not be ascribed to differences in anthropometrical characteristics at baseline.

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### 3.2.2 Total study group analysed by active or placebo ingredients

In this section, because there was no significant difference in demographic characteristics such as age (p = 0.58) and gender (p = 0.35) at baseline between the study groups, female and male data were analysed together.

When the total study group sample was analysed, based on the drug treatment group they were allocated, namely active or placebo, there was no significant weight loss from baseline to follow-up group for either group. The active drug group (N = 48) had a mean weight loss of -0.23kg (SD = 0.21) and placebo group (N = 39) a gain in weight of 0.26 kg (SD = 0.24); no significant difference was found (p = 0.13). The mean fat mass difference between baseline and follow-up measurement for active and placebo group was 0.08 kg (SD = 0.21) and -0.11kg (SD = 0.23) respectively; similarly, no significance was found (p = 0.55). Figure 1 shows that the follow-up measurements did not change significantly from the baseline measurements. This applies to both weight and fat mass measurements.

Table 13: Anthropometric data for active and placebo treatment groups

*Repeated Measures Analysis of Variance test was carried out.

Anthropometric data	Baseline			Follow up			p – value*
	Active	Placebo	Total	Active	Placebo	Total	
	(N = 48)	(N = 39)	(N = 87)	(N = 48)	(N = 39)	(N = 87)	
Weight [kg] (SD)	86.10 (13.07)	82.32 (10.39)	84.40 (12.11)	85.85 (13.23)	82.58 (10.42)	84.39 (12.18)	p = 0.13
Height [m] (SD)	1.63 (0.07)	1.62 (0.06)	1.63 (0.07)	1.63 (0.07)	1.62 (0.06)	1.63 (0.07)	-
Body Mass Index [kg/m^2] (SD)	32.22 (4.05)	31.51 (3.64)	31.90 (3.91)	32.12 (4.06)	31.61 (3.67)	31.89 (3.92)	p = 0.10
Mid upper arm circumference [mm] (SD)	33.92 (2.65)	32.39 (3.59)	33.24 (3.18)	33.75 (2.6)	32.49 (2.83)	33.19 (2.80)	p = 0.30
Estimated Fat mass [kg] (SD)	31.68 (6.47)	31.20 (5.82)	31.46 (6.23)	31.75 (6.55)	31.11 (5.66)	31.46 (6.20)	p = 0.55
Estimated Fat mass [%] (SD)	40.93 (6.24)	37.82 (4.67)	37.25 (4.69)	37.02 (5.02)	37.66 (4.6)	37.31 (4.85)	p = 0.21
Waist circumference [cm] (SD)	100.16 (9.82)	100.25 (7.05)	100.2 (8.74)	99.95 (10.38)	98.77 (7.59)	99.42 (9.31)	p = 0.11

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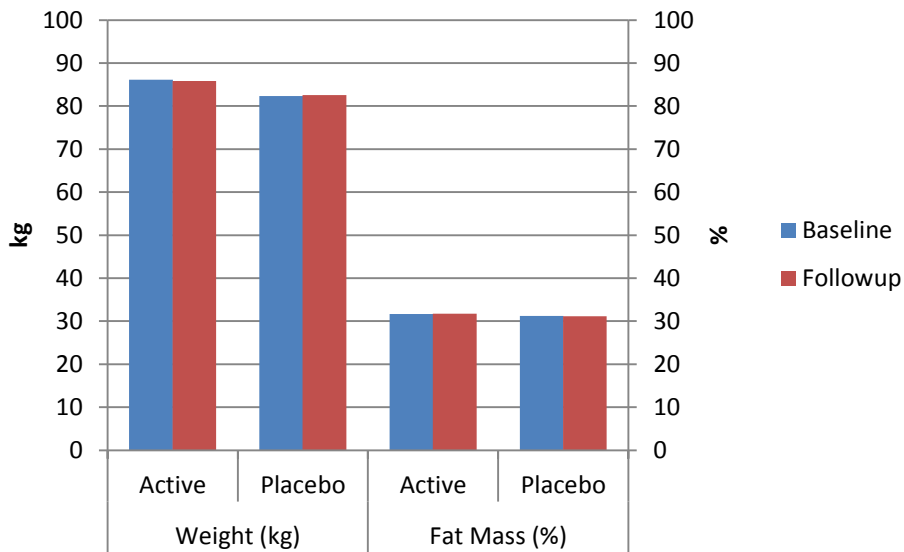
Figure 1: Baseline and follow-up means for weight and fat mass

3.2.3 Total study group analysed by packaging presentation

Table 14 illustrates the anthropometric data of the 2 groups divided according to the type of packaging the product was dispensed in. Baseline anthropometric data changed minimally when compared to the follow up measurement, this was found for both the Bioslim and No Name packaging groups, and the difference between the baseline and follow up measurements was determined. No significant difference was seen between the mean weight difference of the Bioslim packaging group (mean difference = 0.11kg, SD = 0.23), and the Bioslim dispensed in No Name packaging group (mean difference = 0.14kg, SD = 0.22), (p = 0.43). A mean difference for Fat mass of -0.16kg (SD = 0.22) and 0.13kg (SD = 0.22) was recorded for the Bioslim and No Name packaging respectively and it was found not significantly different (p = 0.35).

Table 14: Anthropometric data for various packaging groups

*Repeated Measures Analysis of Variance test was carried out.

Anthropometric data	Baseline			Follow up			p – value*
	Bioslim Packaging	No Name Packaging	Total	Bioslim Packaging	No Name Packaging	Total	
	(N = 43)	(N = 44)	(N = 87)	(N = 43)	(N = 44)	(N = 87)	
Weight [kg] (SD)	85.72 (11.95)	83.11 (12.13)	84.40 (12.11)	85.54 (11.91)	83.26 (12.34)	84.39 (12.18)	p = 0.43
Height [M] (SD)	1.63 (0.07)	1.62 (0.07)	1.63 (0.07)	1.63 (0.07)	1.62 (0.07)	1.63 (0.07)	-
Body Mass Index [kg/m^2] (SD)	32.09 (3.95)	31.17 (3.09)	31.90 (3.91)	32.03 (3.96)	31.76 (3.93)	31.8 9(3.92)	p = 0.35
Mid upper arm circumference [mm] (SD)	33.37 (2.63)	33.10 (3.67)	33.24 (3.18)	33.22 (2.55)	33.16 (3.05)	33.19 (2.80)	p = 0.44
Estimated Fat mass [kg] (SD)	31.47 (6.64)	31.46 (5.88)	31.46 (6.23)	31.34 (6.48)	31.59 (6.00)	31.46 (6.20)	p = 0.35
Estimated Fat mass [%] (SD)	36.68 (5.33)	37.8 (4.00)	37.25 (4.69)	36.67 (5.37)	37.93 (4.32)	37.31 (4.85)	p = 0.69
Waist circumference [cm] (SD)	99.59 (7.49)	100.8 (9.86)	100.2 (8.74)	99.27 (9.13)	99.58 (9.58)	99.42 (9.31)	p = 0.24

3.2.4 Total study group analysed by combining the effect of packaging and ingredients.

Anthropometric data were analysed according to the 4 groups that subjects were randomly assigned to at the start of the trial. Each group was influenced by the combination of two variables, namely packaging and ingredient as listed in Table 15.

Figure 2 represents the difference in anthropometric measurments between baseline and follow-up for the 4 treatment groups. No significant difference between the four groups in weight (kg), fat mass (kg) and waist circumference was found. Two groups received the active ingredient (yellow and orange) and two groups received the placebo (green and red) and no trend was found between the groups. Only the yellow group had a mean loss in weight (-0.45kg), the remainder had either no weight loss or an increase in weight. Fat mass showed a relatively minuscule change and only the red group achieved a loss in fat mass (-0.30kg).

Contradictory to the weight difference finding, all groups had a mean waist circumference loss except for the yellow group (0.54cm).

Table 15: Anthropometric means and standard deviations for the 4 study groups

4 Study Groups	Weight difference (kg) (p = 0.30)	Fat mass difference (kg) (p = 0.76)	Waist circumference difference (cm) (p = 0.15)
Yellow (Active drug with Bioslim packaging)	-0.45 (1.67)	-0.02 (1.36)	0.54 (4.84)
Orange (Active drug with No Name packaging)	0 (1.44)	0.18 (1.56)	-1.09 (2.49)
Green (Placebo with No Name packaging)	1.29 (1.32)	0.08 (1.27)	-1.36 (2.63)
Red (Placebo with Bioslim packaging)	0.24 (1.35)	-0.30 (1.36)	-1.64 (2.97)

Table 15 shows anthropometric means and standard deviations for the 4 study groups, where weight, fat mass and waist circumference differences were derived from taking the value at follow-up less the baseline value. All negative signs indicate a loss in mass or centimetres at the end of the study period. No statistical significance was found between the 4 treatment groups, as weight difference (p = 0.30), fat mass difference (p = 0.76) and waist circumference (p = 0.15) were all greater than (p = 0.05).
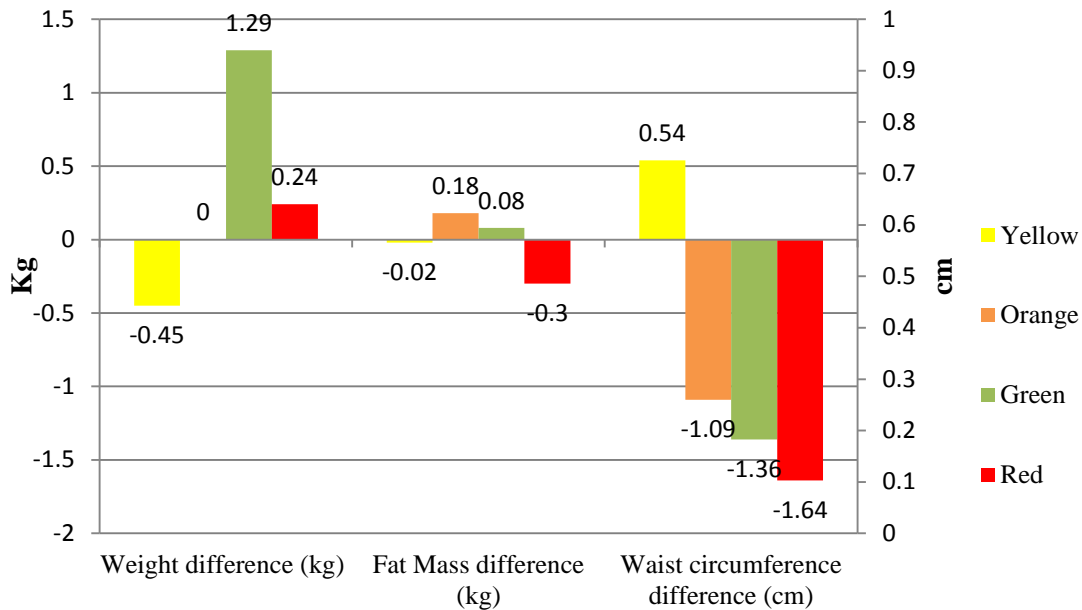
Figure 2: The difference in anthropometric measurements between baseline and follow-up

Yellow = Active drug, Bioslim packaging

Orange = Active drug, No Name packaging

Green = Placebo, No Name packaging

Red = Placebo, Bioslim packaging

3.3 Questionnaire

3.3.1 Subjects' perception of the effectiveness of Bioslim

As many as 72% of the subjects were confident of the effectiveness of Bioslim at the start of the trial. This confidence seemed to have been engendered by marketing, which entails packaging, testimonials and advertising, since it was the most common factor leading subjects to believe in Bioslim's effectiveness. Figure 3 illustrates the factors that influenced subjects' perception, which prompted them to believe in the efficacy of Bioslim, without having prior experience with usage of the product. Marketing was definitely the domineering factor that influenced subjects' perception of the efficacy of the product, with 59% of the subjects agreeing that Bioslim was effective, based simply on their marketing. This finding was further confirmed by the significant difference found between the Bioslim packaging and No Name packaging group, when comparing non-believers to believers (chi-square test, $p = 0.04$).

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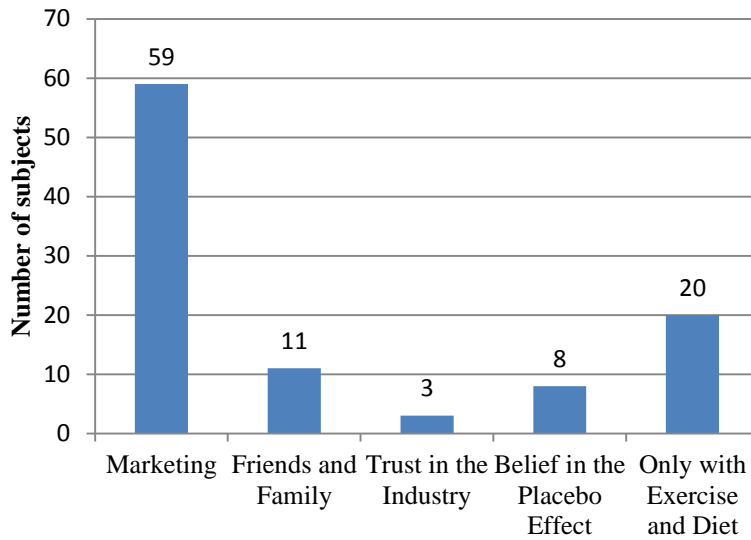
Figure 3: Factors influencing subjects' perception of the efficacy of Bioslim

3.3.2 Consumers' satisfaction with the usage of weight-loss products

In this study, 42 (48%) subjects reported having used other weight-loss drugs previously (see Figure 4). The most commonly used products included Leanor (n = 6) and Herbalife (n = 6). Out of the 42 subjects who had previous experience, only 17 (40%) subjects were satisfied with the result. Here, satisfaction is defined as the product meeting the subjects' expectation and having the desired effect, namely weight loss. Similar results were found regarding subjects' experience with Bioslim in the study, as only 33% (n = 29) reported being satisfied, with the remaining 67% unsatisfied. Of this group, 83% (n = 24) reported being unsatisfied because of their failure to detect any significant weight loss.
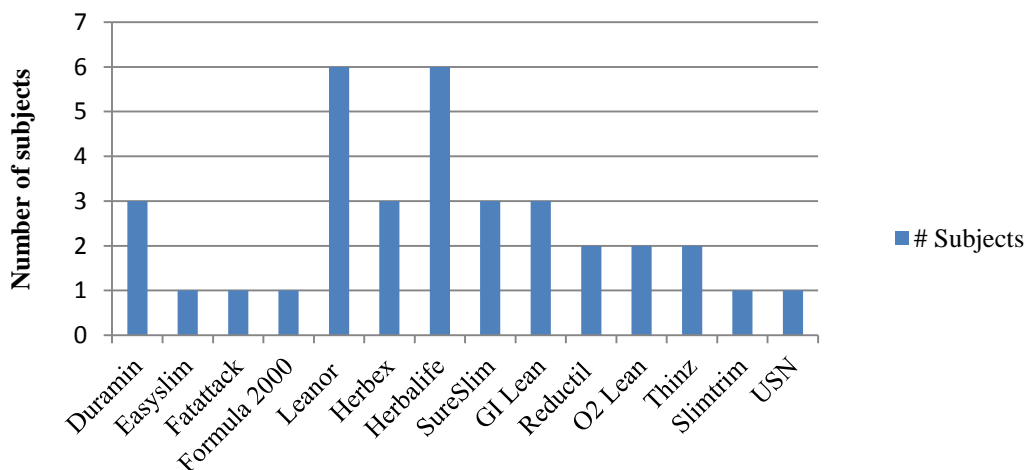
Figure 4: Weight-loss products used by subjects before joining the study

3.3.3 Exercise

Assessment of the questionnaire comparing the Bioslim and No Name packaging group shows that packaging did not promote subjects' inclination to exercise (chi-Square test, p = 0.59), as 23 subjects from the Bioslim packaging group and 21 subjects from the No Name packaging group answered yes to exercise during the trial. In addition, the mean exercise time for those who did exercise was 176.96 minutes (SD = 21.15) in the Bioslim packaging group and 135.48 minutes (SD = 110.04) in the No Name packaging group. Although the fat mass reduction was clinically minimal, the length of time spent on exercise by the total study group correlated significantly with fat mass reduction (r = -0.31, p = 0.004). Furthermore, when data was analysed separately as active (n = 48) and placebo (n = 39) groups, the active drug group (see Figure 5) reveals an even stronger correlation (r = -0.45, p = 0.0012), while the placebo drug group showed an insignificant, weak correlation (r = -0.05 p = 0.77). The same was not reflected in weight loss (r = -0.007, p = 0.95) and waist circumference difference (r = -0.08, p = 0.45), where there was no significant correlation to length of exercise, despite weight difference, and fat mass difference being significantly correlated (r = 0.48, p = 0.00).
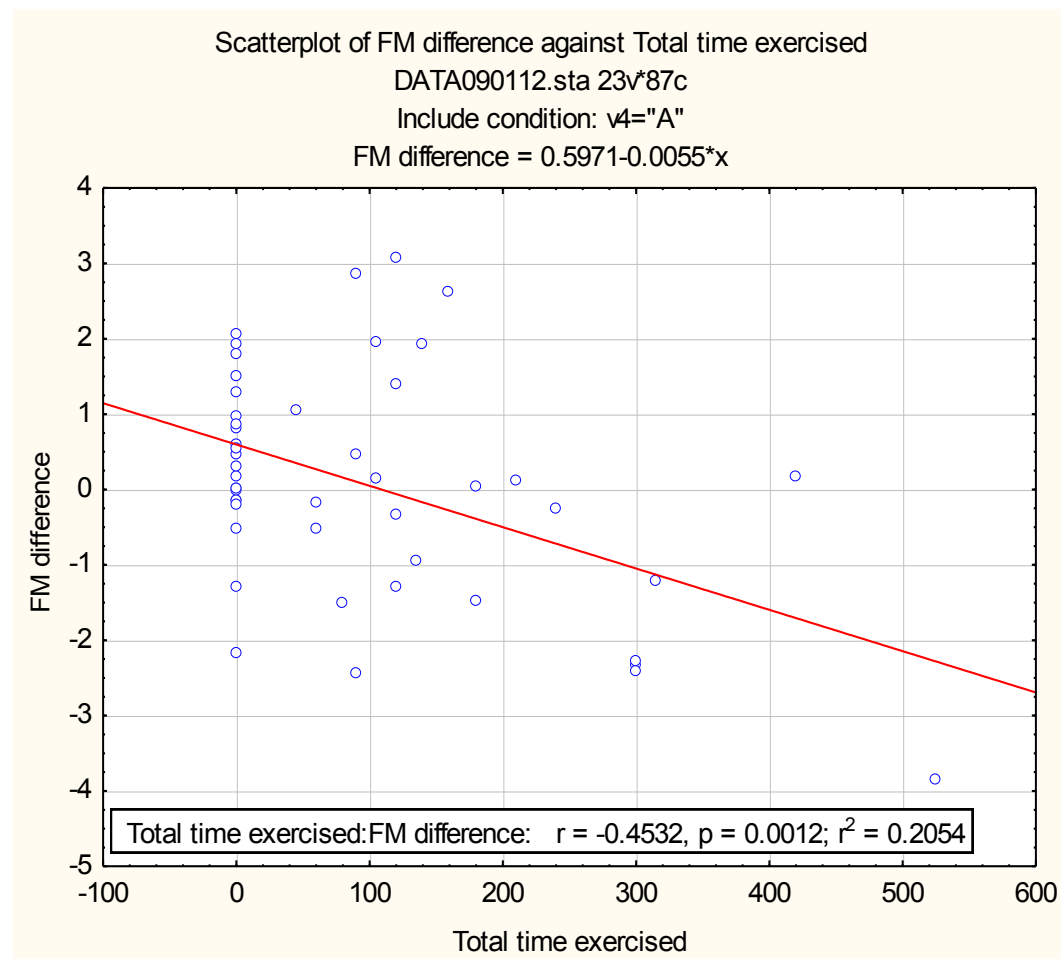
Figure 5: Fat mass difference against total time exercised (minutes).

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3.3.4 Diet

Fifty-four out of 87 (62%) subjects did change the way they ate during the study to try and lose weight. This did not have a significant impact on weight (p = 0.31), fat mass (p = 0.95) or waist circumference (p = 0.31). The subjects' decision to change their diet was not influenced by the packaging (p = 0.89), nor the disclaimer/instruction on the packaging, nor the type of pills (p = 0.42) that were administered.

The most common way in which subjects' reported changing their diet was to cut down carbohydrate intake (see Figure 6). This is compared to other macronutrients, where increasing protein consumption was mentioned only once and reducing fat intake was mentioned 10 times.

All subjects were provided with the same menu plan, as found in the Bioslim packaging, but only 34 subjects made use of this plan and only one out of the 34 claimed to have succeeded in following the diet, defaulting less than 4 days during the one month study period.
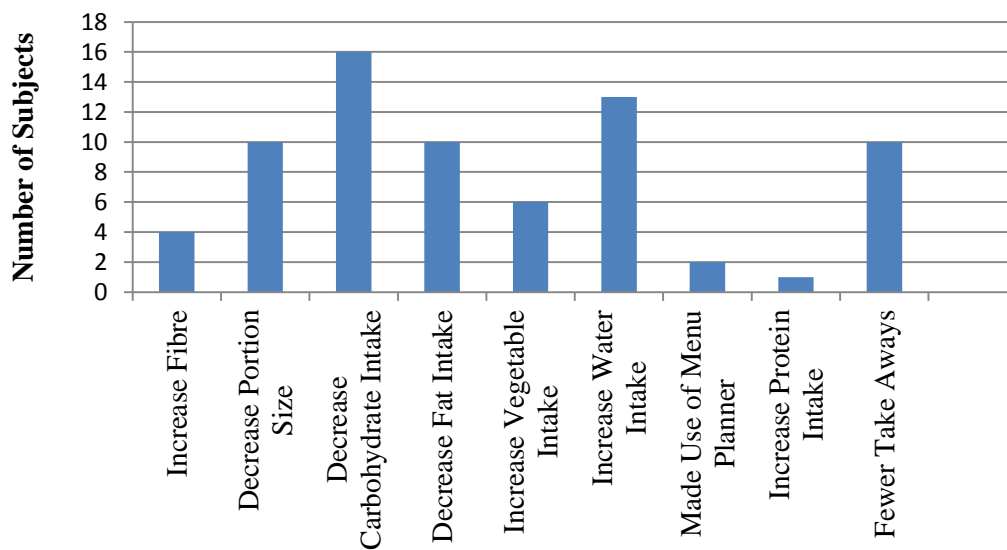
Figure 6: Ways in which subjects claim to have changed their diet during the trial

Participants mentioned, "decrease in carbohydrate intake" (n = 16) as the most frequent response, "increased water intake" (n = 13), and "less take-out", "decrease in fat intake" and "decreased portion size" (n = 10).

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3.3.5 Side effects

Nine of the 87 (10.34%) subjects reported various side effects: heart palpitation (n= 1), dry mouth (n = 2), increased appetite (n = 1), constipation (n = 3), nausea (n = 1), gaseous stomach (n = 1) and fatigue (n = 1). Three out of the 9 subjects who reported side effects were receiving active pills. Table 16 contains a list of side effects reported by subjects and their frequency, including the types of packaging and ingredients each subject was receiving. In total 3 out of 9 (33%) subjects who claimed to experience some side effects, were on active ingredients and 5 out of 9 (66%) subjects received Bioslim packaging. The individual who had experienced heart palpitations was on active drug and No Name packaging.

Table 16: List of side effects reported by subjects and their frequency, based on the type of packaging and ingredients each subject was receiving.

Side effect	Number of subjects affected	Pill type		Packaging type	
		Active	Placebo	Bioslim	No Name
Heart palpitations	1	1	0	0	1
Dry Mouth	2	0	2	1	1
Increased appetite	1	1	0	1	0
Constipation	3	0	3	1	2
Gaseous stomach	1	1	0	1	0
Nausea	1	0	1	1	0
Fatigue	1	0	1	0	1

Chapter 4

Discussion

4.1 Efficacy of Bioslim as a weight-loss dietary supplement

The efficacy of Bioslim was evaluated by comparing the subjects receiving Bioslim (the active treatment group) to the placebo group, to ascertain if there were any significant differences in anthropometric changes from baseline to follow-up measurement. The intervention period was chosen as one month, as this is the period over which Bioslim advertised efficacy. The results show that although the active treatment group subjects did loss a marginal amount of weight, and the placebo group had a slight increase in weight over a period of one month, the difference in weight changes was not significant (p = 13).

Similar outcomes were observed for fat mass and waist circumference; none of the anthropometric measures revealed any significant differences between the active and placebo groups. Female and male subjects were not analysed separately, as at baseline it was found that the study groups were not significantly different to each other with regard to both demographic and anthropometric characteristics. In other words, male and female subjects were equally distributed between study groups.

The lack of efficacy of Bioslim as a weight-loss dietary supplement found in this study is supported by previous reviews on dietary supplements which are used for anti-obesity purposes, in which no supplement was found to be effective in reducing body weight [131, 132, 133].

The two main ingredients in Bioslim are pyruvate and *Citrus aurantium.*

The study by Pittler *et al.* [133], which tested pyruvate on its own, at a daily dose of 6g and which included exercise and an energy restricted diet for the 6 week trial period, found that pyruvate did not have an effect on weight reduction when compared to a placebo group. Bioslim contains only one thirtieth of that dose; in addition exercise and diet were not compulsory for this study.

Trials investigating the efficacy of *Citrus aurantium,* made use of *Citrus aurantium* at a much higher dosage than the 230mg found in Bioslim or ephedrine was incorporated as one of the active ingredients to further increase the adrenergic stimulatory effect [69, 77, 78, 79].

The equivalent amount of synephrine alkaloid found in *Citrus aurantium* from these trials is 5-14mg per day. It was noted by Haaz *et al.* [61] that no serious adverse events were reported at this dose, but that it may be too low to serve as an effective weight-loss supplement, unless used in conjunction with ephedrine. According to Jones *et al.* [77] 1 mg/kg/day is potentially a safe and efficacious dose of synephrine alkaloid, taking into consideration that 1000 mg per

day is the minimal lethal dose for an adult, according to *Martindale: The Complete Drug Reference* [134]. The dose frequency of Bioslim (once a day) may also be the reason for the lack of efficacy found in this study. Synephrine alkaloid is readily absorbed after oral ingestion and reaches plasma peak in 1-2 hours, its half-life being 2-3 hours. This would suggest that, a regimen of a dose of three times a day would be required for it to be effective [135].

In conclusion, when investigating the two key active ingredients of Bioslim, pyruvate and *Citrus aurantium*, it was found that previous studies did not support efficacy in weight loss. The results of this study confirm these findings. Pyruvate and *Citrus aurantium*, the active ingredients of Bioslim, did not have any significant weight-loss effect in the active-ingredient group when compared to the placebo group. Furthermore, even if these two ingredients are potent weight-loss enhancers, the dose and dosing frequency of Bioslim is neither comparable nor sufficient to induce any weight loss.

4.2 Consumers' confidence in the weight loss product

Seventy-two percent of the subjects considered Bioslim to be an effective dietary supplement for weight loss at baseline, demonstrating significant confidence in the product. This finding correlates with the results of a US national survey, which showed that 63% of subjects who used dietary supplements believed that they are effective weight-loss products. Furthermore, 49% believed that all dietary supplements are tested by a government agency for efficacy [136]. This is clearly a misconception, as in both the USA and SA, no regulations are in place to monitor the efficacy or the safety of dietary supplements currently available to the general consumer. The dietary supplement market is fast-growing and lucrative. Consumers spent R889 million in 2003 (the most recent data available) on products whose efficacy has not been proven, and more importantly, whose safety profile is unknown [137].

Clinical guidelines recommend that successful weight loss and maintenance require physical activity and lifestyle changes [64]. However, such interventions are difficult to follow, as they require much effort and discipline. As a consequence, consumers are in search of alternate quick-fix methods, which in turn fuel the dietary supplement market, since most products advertise to accomplish just that. These products are available to the consumer without the need for a prescription, making them easily accessible. They are aggressively advertised, and furthermore, they are often cheaper than prescription weight-loss drugs and do not require the payment of consultation fees to a doctor. The US national survey also found that 67% of subjects do not seek weight-loss assistance from a doctor and 69% admit that they fail to report their concomitant use of dietary supplements to their doctors [136]. This is worrisome, as obesity is regarded as a disease, and like all other chronic diseases of lifestyle, it is associated

with "hidden" secondary sequelae. The assistance of professional health carers is vital to ensure efficacy and safety of weight loss attempts**.**

In this study, marketing was one of the most compelling reasons for believing in the efficacy of Bioslim, as 59% who were confident in Bioslim's efficacy said their belief was based on Bioslim's marketing material such as testimonials shown on television advertisements or the attractive packaging. One of the inclusion criteria was that all subjects were required to have heard of Bioslim before entering the study, either via word of mouth or by encountering Bioslim marketing materials, but not to have actually used the product. This does not mean that the reason people joined the trial was because of their interest in Bioslim, as no mention of Bioslim appeared in the local newspaper advertisement recruiting subjects. To further illustrate the power of marketing on consumer perception, it was found that subjects who received the branded package in this study had a significantly greater confidence in the efficacy of Bioslim when compared to subjects who received No Name packaging.

Bioslim's aggressive marketing schemes often include testimonials to illustrate the product's efficacy rather than the use of sound clinical trials. This study's results indicate that marketing is, without a doubt, a useful method of enticing the consumers to believe in the efficacy of the product, which in turn, leads to the purchase of the product. An increase in sales also leads to increased funding to fuel marketing schemes, as can be seen by the 189% growth in the amount spent on advertising dietary supplements in South Africa in 2001, a total of USD 944 million, reaching USD 2.7 billion in 2005 [138].

In a study by Pillitteri *et al.* [136], the use of dietary supplements for weight loss was found to be more common in females, younger adults, individuals with a lower educational level and subjects with lower incomes. In this study, more females than males enrolled in the study which could be anticipated, since previous studies have shown that weight-loss products attract more attention from South African females, as they are more concerned with body image [35]. What is concerning, is that lower income individuals could possibly spend more money on weight-loss products, with little efficacy, because of the media influence, rather than buying healthy, nutritious food and receiving individualised health advice concerning weight-loss from professionals such as dieticians.

4.2.1 The effect of marketing on the placebo effect and the possible enhancement of Bioslim's efficacy

In this study, subjects were randomised to receive one of the four treatments. Each group was influenced by a combination of two variables: packaging (either No Name or Bioslim packaging) and the pill components (either with the active ingredient or a placebo). It was

found that there were no significant differences between the groups when comparing weight, fat mass and waist circumference changes after the 4 week trial period. It was originally postulated that due to Bioslim's aggressive weight-loss campaign, its intense advertising would foster a greater false expectation of effortless weight loss, without much change in diet or in exercise regime, than an unbranded placebo would. This study postulated that advertising may increase the placebo effect and evoke physiological reactions, where subjects may subconsciously try harder to exercise more and eat more healthily. As was shown with painkillers, when volunteers took an inert substance and believed that they had been given a potent painkiller, some of the volunteers naturally released opioids in the expectation of pain relief [113]. However, in this study, marketing did not have a significant impact on the placebo effect. One explanation is that the subjects' repeated failure with previous weight-loss attempts, using dietary supplements, may have resulted in lower expectations, therefore reducing this possible influence. Sixty percent of subjects who had previous experience with other weight-loss supplements were dissatisfied with their results and found that these weight-loss supplements made no difference to weight loss. Therefore, even though all of the subjects in this trial had no previous experience with Bioslim, they had shown great confidence in its efficacy, so that one might have expected a noticeable increased placebo effect, but this was not evident. The level of expectation may have been diminished by a lack of conviction in the efficacy of weight-loss supplements in general.

4.3 The potential dangers of using Bioslim

4.3.1 Adverse side effects

Nine subjects (10%) reported adverse side effects whilst participating in the study, including nausea, constipation, dry mouth, and heart palpitations whilst participating in the study. These are commonly associated with the use of ephedrine and synephrine alkaloids [87]. There was no significant difference between the active and placebo group concerning the occurrence of reported adverse events. It should be noted however, that one subject from the active group withdrew from the study because of heart palpitations.

4.3.2 Quality and safety of dietary supplement products

Dietary supplements are often perceived to be safe because they are made from natural herbal ingredients. This was illustrated by a survey that investigated the use of dietary supplements by the general consumer. Results from the survey showed that a third of the interviewed subjects believed dietary supplements are safer to use than prescription drugs [136]. This is not always true as Ephedra, a once popular ingredient in weight-loss supplements and now a

banned substance, is known to raise blood pressure and can be harmful, particularly to people with existing hypertension [72]. Hypertension is also common with weight-loss drug users, as it is frequently found in overweight or obese subjects.

The risk of using dietary supplements is often underestimated, in addition the product quality and accuracy of labelling are also overlooked. An example of this was illustrated in a study by Coffey *et al.* [139] on a dietary supplement that contains ephedrine. They found that the stated quantity of each ingredient was less than half of the actual quantity when compared by two independent lab analyses of the supplement. This shows that manufacturing control of the product is not as rigorous as one would expect it to be and the quality of the tests conducted on these products is then in question. One study examined 20 ephedra-containing dietary supplements, using liquid chromatography to investigate the actual content versus the label claims. It was found that half of the products showed a discrepancy in excess of 20% between the label and the actual alkaloid content. Not only did the content not match the label information, but it was also found that two lots of the same product were also inconsistent in ingredients. One product did not even contain ephedra alkaloid [140]. This poses a serious concern as the amount in the supplement may reach the toxicity level, contradictory to the level stated on the label, further highlighting the risk of using dietary supplements that are unregulated.

In 2007, the FDA established Good Manufacturing Practices (GMPs) for the dietary supplement industry. This is a process that the manufacturers have to adhere to so that the products are safe, effective and non-toxic. For a manufacturer to fully comply with GMPs, there are certain processes to follow such as quality control of the product, supply and preparation of the raw material and packaging and labelling of the products. Adherence to GMPs needs to be substantiated by third party audits. There are a few elements that need to be tested to ensure good compliance; these are identifying the materials, product stability over time, contaminant testing and potency assays [141]. These elements were not tested in this study, as it was not an objective of the study to quantify the ingredients of Bioslim pills or to determine whether the content matched the labelling.

In South Africa, any dietary supplements which make any medicinal claims and meet the definition of a medicine must be licensed by the MCC for current good manufacturing processes as part of the registration process. According to the Medicines and Related Substance control act, 1965 [96], Bioslim is regarded as a medicine and yet, according to the author's understanding, Bioslim is not licensed by the MCC nor required to comply with good manufacturing processes.

4.4 Physical activity

4.4.1 Correlation between exercise and body composition.

Although other factors play a role in the gaining or losing of weight, simplistically it can be considered as a result of the difference between energy intake and energy expenditure. A negative energy balance, due to higher energy expenditure, such as an increase in physical activity, will result in loss of weight [142]. Subjects in this study demonstrated that the amount of time spent on exercising was significantly correlated to the amount of fat mass lost ($r = -0.45$, $p = 0.0012$). This correlation was only found in the active group. In the placebo group, the same correlation was not found between time spent on exercising to fat mass lost ($r = -0.05$, $p = 0.77$). Therefore, subjects who are on Bioslim may lose more fat mass when they exercise. However none of the subjects in this study lost a significant amount of fat mass after taking the product for one month.

Interestingly, even though weight and fat mass were significantly correlated in the active group ($r = 048$, $p = 0.00$), weight and time spent on exercise were not significantly correlated in the active or placebo group. A systematic review by Kay *et al.* [143] explains that physical exercise can change body composition without the reduction of body weight. As exercise improves body composition by reducing fat mass and increasing fat free mass, this factor is more pertinent to reducing metabolic and cardiovascular health risks than actual weight loss [143].

Furthermore, when examining the effect of packaging or marketing on the subjects' behaviour, it was found that whether subjects received the Bioslim packaging or the No Name packaging, made no difference to the total time they spent exercising. Therefore, the actual Bioslim packaging does not motivate subjects to exercise harder and as a result lose more weight. Although a high percentage (72%) of subjects in the group who received Bioslim packaging, were confident in the effectiveness of Bioslim, it appears that their confidence in the product, prompted by marketing, did not motivate them to improve their lifestyle choices to enhance weight loss. Subjects relied purely on the product itself, and did not consider their own lifestyle changes as necessary for contributing and encouraging weight loss, even though the package assertion says, "Only effective when used in conjunction with a kilojoule-controlled diet and moderate exercise". One possible explanation is that the advertisement for from Bioslim persuasively suggests that the product itself is so effective that consumers do not need to restrict their dietary intake or increase their physical activity.

4.4.2 Weight maintenance and exercise

Exercise plays a pivotal role in the treatment of those who are overweight and obese, as well as preventing weight regain after successful weight loss[131]. However, more and more people are adopting a sedentary lifestyle, relying heavily on motor vehicle transport and entertainment that does not require physical activity. Measurement of physical activity faces various challenges, and as a result there is a lack of quality data correlating the relationship between physical activity and obesity. Self-reporting methods are often adopted because of their convenience, instead of the use of objective measurements, which often provide a more realistic perspective. Physical activity assessment is also multifaceted; one needs to consider intensity, frequency, duration, and the type of activity that took place. Even in the absence of direct evidence to support this statement, there are observational data to indicate the importance of exercise in weight-loss [144].

A study by Steyn *et al.* [145], investigating chronic diseases of lifestyle in South Africa, found that dramatic lifestyle changes occur when rural dwellers move to urban areas. It was found that the change in their environment reduced their physical activity level and the transition in nutritional intake was associated with the increased prevalence of overweight and obesity. In rural areas physical activity is part of life, and since motor vehicle transport is rarely available, villagers will walk to school and to health facilities which are often far away. However, as transport has become more readily available and television and electric appliances are now regularly found in homes, more time is spent on sedentary activities [145].

The decline in physical activity levels is one of the major factors contributing to the rising obesity epidemic, impacting not only the developed, but also the developing world, including South Africa [146].

It has been shown that physical inactivity is associated with an increased risk of mortality and morbidity resulting in coronary heart disease, stroke, diabetes, cancer and mental illness such as depression [147]. In contrast, exercise in overweight and obese individuals substantially reduces disease risk and healthcare costs. It is possible to be overweight and physically fit at the same time, reducing morbidity risk; exercising then is not only for the purpose of weight loss [148].

The pertinent question is, exactly how much physical activity is required for the prevention of weight gain or weight regain? The main guideline recommendation, according to the US Center for Disease Control and Prevention [146], is that sedentary adults should accumulate 30 minutes or more of moderate-intensity physical activity every day of the week. This

recommendation is targeted for the improvement of health by increasing cardiovascular fitness. However for prevention of weight gain or regain, the US Institute of Medicine (IOM) recommends 60 minutes of moderate-intensity physical activity on a daily basis [149]. In a prospective study by Shoeller *et al.* [150], using DLW (double labelled water), it was found that one year after obese subjects lost their weight, those who had a physical activity level (PAL) of 1.75 (where PAL of 1 indicates resting metabolism) regained the least amount of weight. A physical activity level such as this translates into 60 minutes of moderate intensity activity, in line with IOM's recommendation.

Physical activity alone, without energy restriction, has been shown to induce fat loss and an increase in lean body mass, rather than a total weight reduction [151]. However, when it comes to weight maintenance, over 50% of individuals who lose weight purely on energy restriction, regain the weight that was lost. This could be because dietary restrictions are difficult to sustain over time and such deprivation can result in a reduced resting metabolism to counter the effect of reduced energy intake [142]. Donnelly *et al.* [142] further state that exercise is one of the greatest predictors for weight maintenance for those who have lost weight previously.

4.5 Dietary intake

Sixty-two per cent of the subjects in this trial attempted dieting by either increasing their fibre intake, cutting back on carbohydrates, minimizing take-aways or by reducing portion sizes. This change in dietary behaviour does not seem to have been influenced by the packaging of the product they received, as there was no significant difference found between "No Name" packaging and "Bioslim" packaging groups, when comparing subjects' dieting attempts. The effect of dieting did not have any impact on any of the anthropometric measurements either. It is interesting to note that only 62% of subjects decided to follow the guideline, "Only effective when used in conjunction with a kilojoule-controlled diet and moderate exercise" (which could be found in small print on all of the products given out regardless of which packaging subjects received). The MCC stipulates that this guideline is mandatory for all manufacturers selling weight-loss supplements. However, Bioslim marketing material which is often broadcast on TV can be seen to contradict this guideline for making life-style changes, leading the consumers to often ignore the "fine" print and to rely on the product alone for weight loss. These adverts strongly insinuate that diet and exercise are not required and that the consumers can rely on Bioslim's efficacy alone.

When asked what dietary changes subjects made, "cutting back carbs" was the most frequent response. Correlating to USA data, a very low carbohydrate diet and a high lean protein intake is a popular method of attempting to lose weight. A diet such as this recommends that

the majority of energy should be obtained from protein and fat sources, while carbohydrate intake should be kept to a minimum. Thus the dietary intake of carbohydrates no longer supports normal glycolysis, i.e. using glucose as the normal substrate to provide fuel for the body. When the glycogen or glucose stores are depleted, the body uses ketones, the product from lipolysis, as its main source of energy.

There are different variations of the low-carbohydrate diet, but it is generally defined as a diet allowing a maximum intake of 30-60g of carbohydrates per day without any restriction on energy intake. Some promote increased intake of fatty foods such as bacon, fried eggs and steak, as well as the avoidance of cereal, fresh fruit and starchy vegetables [152]. Other low-carbohydrate diets advocate lean protein sources and up to 100g/day low GI starches. These diets are in contrast to prudent dietary recommendations by health authorities such as the American Diabetes Association (ADA) diet, which advocates that less than 30% of daily total energy should be from fat, 50-55% from carbohydrates and 10 - 20% from protein [153]. In addition, South African prudent dietary guidelines recommend that 50 - 60% of total energy should be from carbohydrates, 30% or less from fat, and protein should constitute 12 - 15% of total energy intake [154]. Restricting carbohydrate intake will shift the total energy distribution between the macronutrients, and as a result most energy intake will be from fat and protein. Increasing fat intake to compensate for the low carbohydrate energy sources increases the risk of developing an unfavourable lipid profile and the risk of micronutrient deficiencies [152].

A meta-analysis of randomised controlled trials compared low-carbohydrate diets to low-fat diets and found that although low-carbohydrate diets are a popular alternative, they show no additional benefit in weight loss effect over low-fat diets after one year [155]. A study by Foster *et al.* [156] found that a low-carbohydrate diet was more effective for weight loss after 3 to 6 months than a low-fat diet, but no difference was found after one year. In addition, most trials are too short to accurately examine the cardiovascular morbidity or mortality. When surrogate markers such as LDL-cholesterol, HDL-cholesterol and triglyceride levels were measured to predict cardiovascular risks, it was found that low-carbohydrate diets increased the LDL-cholesterol level, but favourable changes were found in the other two markers. It is unclear whether the favourable changes in HDL-cholesterol and triglyceride levels would outweigh the increase in LDL-cholesterol [155]. However, trials on high carbohydrate, reduced-fat diets used in conjunction with lifestyle modifications, showed long-term maintenance of the weight lost and lowered the risk of developing type 2 diabetes [152]. The meta-analysis study also examined the adherence level and it was found that both groups had a substantial dropout rate after 1 year, between 31% and 48% in the low-carbohydrate group and between 37% and 50% in low-fat group. As was shown in a one year trial investigating four diets, namely,

Atkins (a very low carbohydrate diet), Zone (a moderately low carbohydrate diet), Weight Watchers (a moderately low fat diet) and Ornish (a very low fat diet), the success of a weight-loss diet is associated more with the subject's adherence to the diet than the macronutrient distribution of that particular diet [157].

A review article on low-carbohydrate diets found that weight loss is predicted by energy intake, diet duration and baseline weight, but not by carbohydrate content [151]. This is probably because it is not palatable, nor possible, to consume such a large amount of protein and fat constantly in real life. As a result, one consumes less energy than usual. Common short-term side effects include constipation, fatigue, halitosis, headache, thirst, polyuria and nausea [151]. It is also easy to mislead the general public towards a poor perception of carbohydrates with common terms such as "carbohydrates make you fat". Although it is not the main objective of this study to examine the popular dieting methods of South Africans, this finding may suggest a poor understanding of healthy dieting guidelines.

4.6 Attrition rate

At the start of the study, a total of 110 subjects were recruited, however only 87 subjects completed the trial. The dropout rate of 20.9% in this study is similar to the 16% of another study by Coffey *et al.* [139], which had a similar methodology, but utilised other ingredients and ran for 12 weeks. Both studies were randomized, placebo-controlled trials that studied the effect of dietary supplements on weight loss. The majority of the dropouts were as a result of subjects not being able to complete the trial: 12 subjects did not complete the trial due to non-compliance or missing tablets and 10 subjects did not return for the follow-up visit. One subject from the active group withdrew due to adverse events. This subject reported severe headache and heart palpitations. Data from a review article investigating factors associated with attrition rate showed that practical difficulties such as a full-time job can influence subjects' ability to be compliant [158]. In the South African setting specifically, the non-affluent population may not always have enough money for transport to return for the follow-up visit. Non-compliance may result from a lack of motivation or lack of confidence in their ability to lose weight [158]. These factors can be attributed to previous weight-loss attempts and continuous failure, demotivating subjects. The high initial weight-loss goal is also significantly associated with a high attrition rate, since such expectations are often unrealistic and not met by the product. Persuasive and effective advertising can further escalate expectations, where subjects are made to believe quick weight loss is possible without much effort. Consequently, most consumers are unhappy with the outcome of the weight loss product, as it does not live up to the effects 'guaranteed' in the advertisement. The QUOVADIS, an observational study on the quality of life in treatment-seeking obese patients

demonstrated the same phenomenon, in which 25% of the dropouts were found to be to the result of dissatisfaction with the results [158].

A high attrition rate compromises the internal validity of the study. As a result, one cannot accurately state that the observed result is solely due to the independent factor, as other confounding effects may have been involved. Such bias cannot be corrected by any form of analysis; therefore the results of this study should be interpreted with the attrition rate in mind [159].

4.7 Shortcomings and limitations of the study

The sample size for this study was 87, which poses as a limitation on the findings. An increased sample size could have increased the significance of the findings, and allowed for possible adverse effects that occur infrequently.

The other limitation of this study was that subjects with diseases of lifestyle, such as hypertension and diabetes, commonly associated with overweight and obesity, were excluded. It was necessary to exclude these potential subjects to ensure their safety, as some of the ingredients in Bioslim can increase cardiovascular risk. As a result, this prevented us from generalizing the findings to the general population who make use of dietary supplements for weight-loss and acquire them over-the-counter with no prescription required.

Physical activity and diet were not closely examined in this study and served as a limitation on the finding. The study's main objective was to investigate as closely as possible the general consumers' behaviour after purchasing over-the-counter weight-loss products, therefore no dietary or physical exercise intervention could be included.

Lastly, the duration of this study was one month. This study time may have been too short to detect side effects associated with the long term usage of Bioslim, or to observe more possible weight loss amongst subjects in the Active group. However, the short duration of this study coincides with Bioslim's claim that it is effective after only one month.

4.8 Conclusions

There was no significant difference in anthropometric changes found between the active and placebo group. From the study result, it is concluded that in the short term, Bioslim is not an effective weight loss supplement. This finding is congruent with studies on other dietary supplement products for weight loss purposes, where none was found to be effective as a weight loss supplement [131, 132, 133].

However, this study has shown that Bioslim may promote fat mass loss during exercise, as only the active group showed a correlation between fat mass loss and the time spent on exercising. The actual clinical benefit of this is uncertain however, as none of the subjects in this study lost a significant amount of fat mass after taking Bioslim for a period of one month.

In contrast to the results found in this study, the majority of the subjects showed great confidence in the efficacy of Bioslim, specifically in the group that received Bioslim branded products specifically. Marketing, inclusive of patient testimonials, product packaging and advertisements was found to be the main reason for boosting subjects' confidence in the efficacy of the product. Interestingly, those who showed great confidence in the product did not change their lifestyle choices to promote weight loss, ignoring the package assertion "Only effective when used in conjunction with a kilojoule-controlled diet and moderate exercise". This behaviour could be explained by influential adverts that suggest that weight loss is easy and effortless with Bioslim, and thus dietary changes or exercise are not compulsory.

The safety of Bioslim is still a concern, as one subject in the active group withdrew from the study due to heart palpitations. Subjects with hypertension were excluded from this study; there is no such restriction in the actual market for Bioslim. There are no warning signs or indications that suggest possible danger to the consumer.

Future studies should include a larger sample size to increase the statistical power of the results to detect possible side effects of using dietary supplements.

Chapter 5

Summary, Conclusions and Recommendations

5.1 Summary

It is estimated that 1.3 billion people worldwide are either overweight or obese, which makes it a global epidemic [4]. In South Africa, the problem is further amplified by the double burden of under-nutrition and chronic diseases of lifestyle. The overall prevalence of overweight and obesity is relatively high compared to other African countries, with more than 29% of men and 56% of women in South Africa being classified as overweight or obese [6]. This poses a serious risk of mortality, as WHO lists obesity as one of the 10 leading risk factors for mortality. It further increases the risk of a number of major chronic diseases including hypertension, type 2 diabetes [10] and cancer [16].

An effective weight-loss method is lifestyle change, by increasing physical activity and lowering energy intake. These lifestyle changes are tough to carry out and difficult to maintain, resulting in a soaring increase in searches for easy weight-loss aids [42]. Dietary supplements are one of the many products which exploit the eagerness of consumers to find an effortless weight-loss solution. They are easily accessible as they require no prescription and are heavily marketed to suggest that weight loss is achievable without exercise or diet. Bioslim, the dietary supplement tested in this study, is one such product. The results of this study show that Bioslim is an ineffective weight-loss aid, matching similar, previous studies on weight-loss dietary supplements [131, 132, 133]. Although a significant correlation was found between time spent on exercising and fat mass loss in the group receiving Bioslim, and not in the placebo group, it is concluded that this result is inadequate to indicate clinical benefit.

One of the misconceptions consumers have when using dietary supplements, is that they are considered safe because they are made from "natural" ingredients and thus cannot be harmful [136]. However, various studies have shown that some of these herbal ingredients can be unsafe [88]. Ephedra, which was once a popular ingredient in weight-loss supplements is now banned due to its cardiovascular risk and various adverse events reported [72].

Currently in South Africa, dietary supplements are not regulated by the MCC. This means that no clinical trials are required to ensure the efficacy or the safety of the supplements before they are made available to the general consumer. The hypothesis that the product has no effect on weight-loss was substantiated. This study emphasizes the importance of a placebo-controlled study to test the efficacy of a weight-loss supplement.

The hypothesis that advertising may increase the result of a placebo response was not substantiated.

5.2 Conclusions

It is concluded that Bioslim is an ineffective weight-loss supplement. Subjects receiving active pills evidenced no significant beneficial changes in weight, waist circumference or body composition. Although, more than half of the subjects attempted dieting and more exercise, it was inadequate to make an impact on weight loss. Advertising and claims made on Bioslim packaging did not increase the placebo effect and made no difference to weight loss. Television and magazine advertising for this product had ceased for a long period before the commencement of the study and this may have had an influence on the result.

Although there was no difference in adverse events reported by the active or placebo group, one subject from the active group withdrew from the study complaining of severe headaches and heart palpitations.

This study emphasizes the need for better regulation of dietary supplements for their efficacy and safety.

5.3 Recommendations

This study serves as a seed study in the hope of motivating other studies related to the use of dietary supplements. To the author's knowledge, there have been no other studies conducted in South Africa regarding dietary supplements of any kind. This highlights the need for more research in this area, in South Africa particularly, since herbal medicine is a popular alternative treatment for various ailments including HIV.

It is recommended that future studies include a larger study population to strengthen the study's results. In addition, they should include laboratory analysis of the contents of the dietary supplement, to compare them to the label and to check the product quality.

A retest of the hypothesis that advertising has a considerable effect on weight-loss in a placebo group, by utilising a product at the peak of its advertising campaign is also recommended.

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Appendices

Appendix 1: Advertisement in local newspaper

Weight loss trial

Would you like to participate in a weight-loss trial to investigate the effectiveness of a popular weight-loss drug?

You would be assigned to one of the 4 treatment groups, receiving weight-loss supplements for a period of one month.

If interested in participating please contact

Tina at 0726106929

for more information.

Appendix 2: Consent Form

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:
Double blinded, placebo-controlled, randomised prospective intervention trial; to investigate the effectiveness of Bioslim in weight-loss and the influence of branding and advertising on the placebo response.

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR:
Tzu-Ting Lee

ADDRESS:
Human Nutrition, University of Stellenbosch. PO Box 19063. Tygerberg 7505

CONTACT NUMBER:
0726106929

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Committee for Human Research at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki 2005 , South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

This project will take place in the Western Cape region, where a total of 120 subjects will be recruited. The aim of the project is to look at the effectiveness of Bioslim in weight-loss and the influence of branding on consumers.

You will be randomly assigned to one of the four groups where you would require taking the assigned drugs for a period of one month. There is an equal chance of you receiving products that do not contain the active ingredients of Bioslim (not real Bioslim) or active (real Bioslim). Neither you nor the principle investigator will know which drug you on until final analysis of the data is done. Furthermore, you may or may not experience any weight loss while participating in this study.

Before you start taking the assigned product, you will be weighed and your mid arm circumference, triceps, biceps, supra ileal, subscapular skinfolds and your waist circumference will be measured. These measurements will not cause any pain or discomfort. At the end of the one-month trial, we will repeat these measurements on you again.

Why have you been invited to participate?

You have been invited to participate in this study because of your interest in weight loss supplements and do not possess qualities that may influence you negatively if you participate.

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What will your responsibilities be?

It is your responsibility to ensure that you attend all your appointments made with the investigator. And to take the products as if you would if you had brought them from the shops yourself.

Will you benefit from taking part in this research?

There are no personal benefits here. But the results of this study may be useful for future consumers when considering usage of weight loss supplements.

Are there any risks involved in your taking part in this research?

There are no known risks involved in participating in this study according to the manufacturers of the active ingredient. If you think that a side effect has occur during the taking of these tablets or during this study, please report this to the primary investigator.

But do not participate if you are allergic to Aspirin or if you are pregnant, breastfeeding, diabetes or on any heart medication.

Who will have access to your medical records?

The information that is collected will be treated as confidential information; if the results are published all identities of the participants will remain anonymous.

Will you be paid to take part in this study and are there any costs involved?

There is no remuneration for participating in this study.

Is there anything else that you should know or do?

You should inform your family practitioner or usual doctor that you are taking part in a research study.

You can contact the study primary investigator – Tina Lee, if there is any queries during the participation of this research at 0726106929.

or

You can contact the Committee for Human Research at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study investigator.

You will receive a copy of this information and consent form for your own records.

Appendix 3: Questionnaire

Questionnaire	Participant ID:		Date:		
1) Have you used any weight-loss product before joining this study?				**Yes**	**No**
If yes, continue by answering question 1a, 1b,1c. If no, continue by answering question 2.					
1a) Please name the product(s), duration of use and date of usage:					
1b) Did you experience any negative side effects? (Such as hunger, abdominal pain, headache, thirst, discolouring of urine, fatigue, nausea, diarrhoea or heart palpitation)				**Yes**	**No**
If yes, what were they:					
1c) The outcome was		**Satisfactory**		**None satisfactory**	
If satisfactory, how so:					
If unsatisfactory, how so:					
The following questions apply to this study					
2) The outcome was		**Satisfactory**		**None satisfactory**	
If satisfactory, how so:					
If unsatisfactory, how so:					
3) Did you exercise				**Yes**	**No**
If yes, continue by answering question 3a and 3b. If no, continue by answering question 4.					

3a) How many days per week **(please choose one)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**

3b) How long each session and what type of exercise:		
4) Did you change the way you eat while participating in this study?	**Yes**	**No**
4b) If yes, how:		
5) Did you follow a energy restricted diet	**Yes**	**No**
If yes, continue by answering question 5a. If no, continue by answering question 6.		
5a) Did you follow the diet on the package insert?	**Yes**	**No**
If yes, then was it:	**Most of the time, with 1 or 2 days missed**	**Tried, but failed to continue**

6) Did you experience any discomfort or negative side effect while participating in this study? (Such as hunger, abdominal pain, headache, thirst, discoloring of urine, fatigue, nausea, diarrohea or heart palpitation.)	Yes	No
If yes, continue by answering question 6a. If no, continue by answering question 7.		
6a). What was the adverse event?		
7) Have you missed taking any pills	Yes	No
If yes, how many days:		
8) Did you believe this product would work for you	Yes	No
8a) If yes, why		
9) Have you ever encounter Bioslim advertisements before?	Yes	No