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Research Article

Can Antidiabetic Plants Used in Cameroon Play as Key for the Treatment of Childhood, Adolescent and Adult Obesity?

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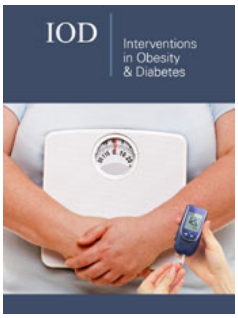

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Abstract

Overweight and obesity are defined as an abnormal or excessive accumulation of fat which can be harmful to health. These are major risk factors for a number of chronic diseases, including diabetes, cardiovascular disease, and cancer. The channel from obesity to diabetes is made by an enlightened deficiency in insulin secretion coupled with an enlightened rise in insulin resistance. Both insulin resistance and defective insulin secretion appear very prematurely in obese patients, and both worsen similarly towards diabetes. Once considered a problem only in high-income countries, overweight and obesity are now on a dramatic increase in low- and middle-income countries. These are major risk factors for a number of chronic diseases, including diabetes, cardiovascular disease, and cancer. Once considered a problem only in high-income countries, overweight and obesity are now on a dramatic increase in low- and middle-income countries. In 2016, more than 1.9 billion adults aged 18 and over were overweight. More than 650 million adults were obese. About 18.5% of children ages 2 to 19 are considered obese in the United States. Cameroon, with 8.6% of its obese population in 2014, is not immune to the upsurge in the number of obese people in the world. In Cameroon obesity is rarely considered as a disease by most traditional healers, especially in the hinterland. Consequently, in this review, we seek to select among antidiabetic plants commonly used in Cameroon those which can play as key for the treatment of childhood, adolescent, and adult obesity. To undertake this objective the below research engines were used to perform a literature search in Google, Google Scholar and PubMed.

a. A given antidiabetic plants used in Cameroon influences the childhood obesity.

b. A given antidiabetic plants with childhood obesity treatment capability.

c. A given antidiabetic plants within adolescence obesity treatment capability.

d. A given antidiabetic plants with adult obesity treatment capability. Ten antidiabetic plants currently used in the treatment of obesity in Cameroon were selected. Only *Allium sativum* was revealed toxic. Four plants among the recorded plants including *Achyranthes aspera*, *Opuntia* spp, *Momordica charantia* and *Gymnema sylvesta* are more effective for the treatment of obesity. However, preventive measures such as healthy nutrition and exercise habits, lifestyle intervention as part of pregnant women and new-born postpartum follow-up care, as well as natural abilities of the body to control obesity are still the best ways to fight against obesity early naturally.

Keywords: Antidiabetic plants; Cameroon; Childhood; Adolescent and adult obesity; Preventive measures; Treatment

Abbreviations: BMI: Body Mass Index; IOTF: International Obesity Task Force; CDC: Center for Disease Control; AHA/NIHHLBI: American Heart Association/National Institutes of Health, Heart, Lung, Blood Institute; T2DM: Type2 Diabetes Mellitus; ACC: Acetil~CoACarboxilase; HMG-CoA: 3-Hydroxy-3-Methylglutaryl Coenzyme A; AMPK: AMP-Activated Protein Kinase; GLP-1: Glucagon1-like Peptide; CRP: C-Reactive Protein; EPA: Eicosapentanoic Acid; DHA: Docosahexaenoic Acid; PUFAs: Polyunsaturated Fatty Acids; CPT1: Carnitine Palmitoyl Transferase 1; TAG-Rich: Triacylglycerols-Rich Lipoproteins; AMP: Adenosine Monophosphate; ATP: Adenosine Triphosphate; SIRT1 (Sirtuin 1): Silent Information Regulator 1; CCK: Cholecystokinin; GLP-1: Glucagon-like Peptide-1; GDH: Glutamate Dehydrogenase; AMPK: AMP-Activated Protein Kinase; PEPCK: Phosphoenolpyruvate Carboxy Kinase; PPAR-γ or PPARG: Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ or PPARG); EAA: Essential Amino Acids; EEA: End-to-End Anastomosis; GDM: Gestational Diabetes Mellitus; ACC: Acetyl-CoA Carboxylase; PP2A: Phosphatase 2A; PGC1-α: Peroxisome Proliferator Activated-Receptor Gamma Coactivator 1-α; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; AST: An Aspartate Aminotransferase; VLDL: Very Low Density Lipoprotein; HDAC: Histone Deacetylase; AD: Alzheimer's disease; PD: Parkinson's Disease; BDNF: Brain-Derived Neurotrophic Factor Regulation; SCN: Suprachiasmatic Nucleus; T3DM: Diabetes Mellitus Type 3; MODS: Multiple Organ Dysfunction Syndrome; LPS: Lipopolysaccharides

Introduction

Terms definitions

Obesity is defined as a BMI equal to or greater than the 95th percentile for children and adolescents of the same age and sex. BMI is calculated by dividing a person's weight in kilograms by the square of his height in meters. For children and adolescents, BMI is age and gender specific and is often considered as BMI for age. A percentile here is each of the hundred equal parts of the population subdivided according to the weight distribution as a statistic variable. Childhood obesity is considered as a major issue for its high prevalence and because of its severe consequences on adult health. Overweight and obesity is defined as an abnormal or excessive fat proliferation that presents a risk to health. A Body Mass Index (BMI) over 25 is considered overweight and over 30 is obese [1]. Diabetes is the leading cause of morbidity and mortality worldwide, characterized by the insufficient secretion or absence of insulin for diabetes mellitus type 1 and presence but inefficient insulin for diabetes mellitus type 2. Gestational Diabetes Mellitus (GDM) arises from glucose intolerance, with an onset during the pregnancy. Diabetes and obesity are the leading health problems and mostly age-linked metabolic sicknesses. Obesity is related to the evolution of diabetes mellitus. High concentrations of glycerol, pro-inflammatory markers, fatty acids, enzymes, overweight, pulmonary hypertension, and other obese entities improve insulin resistance in obese population. The pathology of diabetes mellitus comprises the dysfunction of beta islet cells of pancreas leading to deficient managing of blood glucose concentrations. It is connected with lasting impairment, dysfunction, and letdown of several organs. Obesity is a long-lasting, deteriorating, multifactorial syndrome, which has become a severe hazard to public health universally, as the global prevalence of obesity upsurges exponentially over time. It has been well established that obesity is connected with multiple antagonistic cardio-metabolic properties [2].

Recent prevalence

The global prevalence of obesity almost was tripled between 1975 and 2016. The age-adjusted prevalence of obesity in adults from 2017-18 was 42.4%. In 2016, more than 1.9 billion adults aged 18 and over were overweight. More than 650 million adults were obese. Overall, about 13% of the world's adult population (11% of men and 15% of women) was obese in 2016. Cameroon, with 8.6% of its obese population in 2014, is not immune to the upsurge in the number of obese people in the world [3]. However, in Cameroon obesity and overweight are rarely considered as diseases by most traditional healers, especially in the hinterland. Rather they are well-being characteristics. The global prevalence of obesity almost tripled between 1975 and 2016. By 2030, an estimated 20% of the world's population will be obese. In 2019, 38 million children under 5 years were overweight or obese [3,4].

Importance of Obesity in the World Population

Childhood obesity

Childhood obesity has reached epidemic levels in developed as well as in developing countries. Cameroon, with 8.6% of its obese population in 2014, is not immune to the upsurge in the number of obese people in the world. The incidence of childhood obesity is increasing worldwide, and obesity-related comorbidities are concomitantly increasing in the pediatric population. The consequences of childhood obesity can be broadly classified into medical and psychosocial consequences:

I. The medical consequences include:

a. metabolic complications such as diabetes mellitus, hypertension, dyslipidemia, insulin resistance, high cholesterol,

b. non-alcoholic fatty liver disease, as well as mechanical problems such as obstructive sleep, apnea syndrome, asthma, joint problems and musculoskeletal discomfort,

c. orthopedic disorders.

II. The psychosocial consequences include:

a. anxiety and depression

b. low self-esteem and lower self-reported quality of life

c. bullying and stigma

Childhood obesity is associated with significant morbidities, which not only have immediate impact on the health of the obese children, but also significantly increase the risk of morbidities in adulthood. Overweight and obesity are the most studied variables of medicine in children, and there is no official statement on the cut-off for its definition in this population [5].

Obesity in adolescence

Adolescents with a BMI in the top 5% for their age and gender are considered obese. Being in the top 5% means their BMI is 95% higher than that of their peers (at the 95th percentile or above). Obesity is twice as common in adolescents as it was 30 years ago. Although most complications of obesity occur in adulthood, obese adolescents are more likely than their peers to have hypertension and type 2 diabetes. Although less than a third of obese adults were obese in adolescence, most obese adolescents remain obese into adulthood. The factors that influence obesity in adolescents are the same as those in adults. Hormonal disorders, such as an underactive thyroid gland (hypothyroidism) or overactive adrenal glands, can lead to obesity but are rarely the cause. Adolescents whose weight gain is caused by hormonal disorders are usually short-lived and most often have other signs of the underlying disorder. Any obese teenager who is short and has high blood pressure should be tested for Cushing's syndrome, a hormonal disorder. Genetics play a role, which means that some people are at higher risk for obesity than others. Due to society's stigma against obesity, many obese adolescents have a poor self-esteem and can become socially isolated [6].

Adulthood obesity

If an adult BMI is below 18.5, he is in the underweight range. If his BMI is between 18.5 and <25, he is in the normal range. If his BMI is between 25.0 and <30, he is in the overweight range.

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If his BMI is 30.0 or more, he is in the obesity range. Obesity and excess weight increase severe illness like COVID-19, risk; racial and ethnic disparities persist [7]. The problem has grown to epidemic proportions, with more than 4 million people dying each year due to overweight or obesity in 2017. That why the World Health Organization (WHO) has labeled obesity as the new epidemic of the 21st century. Overweight and obesity rates continue to rise among adults and children. From 1975 to 2016, the prevalence of overweight or obese children and adolescents aged 5 to 19 more than quadrupled, increased from 4% to 18% worldwide [8]. According to the World Health Organization (WHO), 13% of the world's adult population is now obese and 17% of children are overweight or obese and obesity is now a global epidemic. By 2030 nearly 40% of the world's population will be overweight and one in five people will be obese. Globally, 144.0 million children fewer than 5 are stunted, 47.0 million children fewer than 5 have been wasted of which 14.3 million were severely wasted and 38.3 million were overweight. Globally, obesity has almost tripled since 1975. In 2016, more than 1.9 billion adults aged 18 and over were overweight. Of these, more than 650 million were obese. 39% of adults aged 18 and over were overweight in 2016 and 13% were obese. Most of the world's population lives in countries where overweight and obesity kill more people than underweight. 38 million children under 5 were overweight or obese in 2019. More than 340 million children and adolescents aged 5 to 19 were overweight or obese in 2016. Obesity is preventable [9].

Importance of obesity

Our environment conditions individual choices. However; obesity is a complex, multi-factorial disease. Its emergence and installation are the result of individual factors but also of the environment in the broad sense - built environment (housing), school, professional, advertising, etc. - which conditions our eating habits and our levels of physical activity and sedentary lifestyle. Recent changes in our societies have made our environments unhealthy because they promote a low level of physical activity, a significant sedentary lifestyle and excessive consumption of high energy density foods. They are thus qualified as obesogenic. The emergence and development of the obesity epidemic has indeed coincided with:

a. a strong growth connected to high calorie foods and drinks rich in fats, simple sugars and salts in the food supply;

b. at the same time the evolution of our lifestyles (rapid urbanization, changes in the world of work) has led to a decrease in the levels of physical activity and an increase in the levels of sedentary lifestyle [10].

Correlation between Obesity and Diabetes

The association between obesity and type 2 diabetes is so mutually dependent that the term "diabesity" was invented. The evolution from obesity to diabetes happens through an advanced lack of insulin secretion coupled with an advanced upsurge in insulin resistance. Insulin resistance and imperfect insulin secretion appear very precipitately in obese patients, and both worsen similarly to diabetes. Thus, the classic "hyperbolic relationship" between insulin resistance and insulin excretion and the "concept of glucose allostasis" keep on prevailing concepts in this specific field of knowledge. An escalation in overall fat, reasonably visceral as well as ectopic fat deposits, is precisely connected with insulin resistance. The amassing of intra-myocellular lipids may be due to an abridged lipid oxidative capability. The capacity to lose weight is linked to the aptitude to oxidize fat. Thus, a family member deficiency in the oxidative ability of fat is responsible for energy redeemable and disadvantaged weight loss [7].

Origin and Difficulty for Defining Obesity in the Pediatric Group

Obesity is considered as a new pathology in the history of Humankind, being the new food security predisposition the one to blame for such a rising wave [10]. In the last century, technological advances and cutting edge science have modified human lifestyle, changing nourishment regimes and physical activity and therefore creating an imbalance between caloric ingestion and energy expenses that are not able to compensate the caloric excess ingested. This spill-over energy is amassed in the adipose tissue establishing itself as obesity which is considered a step closer to the new evolved man: Homo obesus [10,11]. Nowadays Childhood obesity is a major worldwide health problem. The number of obese children in the pediatrics population is even less encouraging, with at least 20 million overweight children of less than 5 years of age [12]. In the United States, the prevalence has increased in the last 30 years, with a 3,8 times for the 6-11 years, adult group (from 4% to 15,3%), and 2,6-fold for the adolescent group (from 6% to 15,5%) [13]. Defining obesity in the pediatric group is a real challenge owed to growth (weight and height) variations in childhood and adolescence. Some writers use only BMI standards to distinguish between overweight and obesity in adolescents; however, Cole et al. [14] published the percentile tables according to age and sex. With these implements, the Center for Disease Control (CDC) has indistinct overweight unitary group 2-18 years of age as BMI equal or above 95th percentile according to age and sex. The term risk of overweight is applied to restricted children with BMI between 85th and 95th according to age and sex, since CDC prefers not to use the term obesity for psychological/social reasons [15,16]. The International Diabetes Federation (IDF) participated in this worldwide debate when in 2005 they published their particular definition, giving specific interest to the impact of culture in the proper diagnosis of the disease and the cut-offs being set for the patients, predominantly since intestinal obesity was now proposed as a fundamental element for its identification [17].

Limited capacity for envisaging obesity outcomes

Overweight/Obesity is the greatest studied variable of MS in children, and there is no official testimonial on the cut-off points for its definition in this population; in fact there is no agreement on the existence of MS in childhood due to its incomplete capability for envisaging outcomes like Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Disease (CVD). Sixty-one percent (61)% of the children with MS lost at least one of the variables during the

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trial, while 25,5% of the children without MS acquired at least one risk factor, defined as "the instability in the diagnosis of metabolic syndrome." Nonetheless, one of the outcomes that have been explored is the risk of adult obesity in the already obese child [5].

Role of AMPK and prevention of future metabolic obesity complications

Around 30% of adulthood obesity begins in infancy, with even poorest consequences than compared to obese adults were narrow. Overweight adolescents have 50%-70% chance to become overweight or obese adults, whereas only 30% of the reedy children will become obese in adulthood [6,17]. Acetil~CoACarboxilase (ACC) is a multi-subunit and huge multi-domain enzyme in greatest prokaryotes and in the chloroplasts of furthermost plants and algae, and in the cytoplasm of most eukaryotes. It extreme important function is to provide the malonyl-CoA substrate for fatty acid biosynthesis [10]. The second enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the conversion of HMG-CoA to mevalonate, which intervenes in the synthesis of cholesterol and other isoprenoids. The enzyme is also found in eukaryotes and prokaryotes [18,19]. These activities can be organized at the transcriptional level as well as by small molecule modulators and covalent modification and ensure the significance of an appropriate and premature intervention to diminish or completely prevent future metabolic difficulties.

For several studies ACC enzyme presents many activities:

a. effect on energy balance,

b. mitochondrial biogenesis,

c. regulation of lipid/carbohydrate metabolism,

d. and modulation of genetic expression.

AMP-Activated Protein Kinase (AMPK) is an energy forager that regulates cell metabolism. When activated by a shortage in nutritional status, AMPK excites the absorption of glucose and the oxidation of lipids for energy manufacture, while deactivating energy-consuming procedures, including production glucose and lipids, to restore energy balance [20,21].

A new therapeutic route for the treatment of childhood obesity

The entire living world has developed the mechanisms necessary for its metabolic adaptation in response to variable external stresses, an essential condition for survival. Whether at the level of the whole organism, where a whole series of hormonal and neuronal mechanisms can act, or at the cellular level, headquarters of a fine metabolic regulation, it is imperative to respond adequately to the modifications of the environment which are necessary to modify energy balance. Energy stresses are varied and include shortages in energy ingestion (deficit in glucose, amino acids, oxygen, etc.) and/or upsurges in energy demand (growth, sports exercise, etc.). The body has many means to respond to these changes, including AMP-Activated Protein Kinase (AMPK), which has freshly been regarded as a metabolic instrument. The role of AMPK as an energy thermostat puts it at crossroads for energy homeostasis, making it fundamental to analyze the signaling pathways involved in energy metabolism, not only for academic purposes but also for therapeutical goals in childhood obesity [5].

Objective

The high prevalence of obesity shows globally that natural body autoregulation is often outdated or malfunctioning. We wonder if the antidiabetic plants used in Cameroon can provide solutions to the problem of obesity which is strongly related to type 2 diabetes. Therefore, the purpose of this work is to analyze the role of antidiabetic plants as an intervention target in childhood, adolescent hood and adulthood obesity, in view of obesity-diabetes link.

Materials and Methods

Inclusion of plants

Plants take in consideration in this work are antidiabetic principally used in Cameroon. Google, Google Scholar and PubMed search for research and review papers on childhood, adolescence, and adult obesity was performed. The below research engines were used:

a. A given antidiabetic plants used in Cameroon influences the childhood obesity.

b. A given antidiabetic plants with childhood obesity treatment capability.

c. A given antidiabetic plants within adolescence obesity treatment capability.

d. A given antidiabetic plants with adult obesity treatment capability.

e. The plants authentication was performed from the Project of the World Flora Online Consortium and at National herbarium of Cameroon.

Results

Natural abilities of the body to control obesity

Mechanism of regulation of food intake: Regulation of food ingestion implicates peripheral signals and central mechanism, which govern behavioral patterns most important for weight gain or weight loss. The mechanism of all input indications is between the "center of satiety" in the ventromedial nuclei and the "center of hunger" in the lateral hypothalamic zone and the fatty indications originate from the pancreas and adipose tissue presented by insulin and leptin, both are intended to stop eating behavior and food intake once energy stores have been replenished. For example, intestinal indications usually control hunger and eating behaviors [22]. Glucagon1-like Peptide (GLP-1) is an incretin that is released by ingestion, inducing the discharge of insulin from β cells and decreasing food ingesting. Peptide YY - a member of the NPY peptide family - is a peptide of 34 amino acids discharged by the

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intestine that interferes with food ingestion and changes intestinal motility (ilea brake), and its discharge depends on the amount of carbohydrate or lipids in the absorbed meal. This molecule obstructs NPY neurons and triggers the POMC population, dropping 30% of food ingestion using the Y2 receptor. PYY is negatively connected with the degree of adiposity with abridged values compared to subjects of normal weight [23]. Ghrelin is a peptide synthesized in the stomach, and it's related with hunger. It exerts its properties via the growth hormone secretagogue receptor in the hypothalamus and brainstem, with the stimulation of linked peptide neurons, which induces reticence of secretory cells.

Physical training and diminution of pregnancy weight gain and risk of cesarean section

Nutrition and exercise are fundamental pillars in the treatment of overweight and obesity and related conditions such as insulin resistance, cardiovascular disease, and cancer, among others. Overweight women are defined as having a high weight before pregnancy between 25 and 29.9 kilograms. Obese women have a BMI of 30 kilograms or more. Nutrition and physical exercise, or a combination of both the two has been found to diminish pregnancy weight gain by 20% and diminish high blood pressure [21]. Nutrition through exercise can diminish the risk of cesarean section, of having a large baby, and of having a baby with severe breathing problems [21]. Nutrition and physical exercise help pregnant women not to gain too much weight during pregnancy [21]. In general, walking is encouraged for overweight or obese mothers [12]. In extreme cases where the BMI exceeds 35 kilograms, prenatal visits are praiseworthy and dietitian visits are recommended. Health choices such as low-fat milk and alternatives, fruits, and vegetables should be emphasized for pregnant women.

Role anti-inflammatory of exercise

It has been advocated that exercise exerts anti-inflammatory properties which are effective in assisting the low-grade inflammation that illustrates adult obesity [24], and it is not different in childhood/adolescent obesity [25,26]. Weiss et al. [27] published that adiponectin inversely associates with C-Reactive Protein (CRP) ranks, while the latter and IL-6 (interleukin 6 is a cytokine belonging to the trio of pro-inflammatory cytokines of innate immunity) were in direct relation to BMI in children. The overweight is associated with raised up white blood count and CRP suggesting low-grade inflammation in these children [28]. Hypo-adiponectinemia has been autonomously connected with metabolic syndrome in teenagers, which has upgraded adiponectin (Adiponectin is a protein hormone and adipokine, which is involved in changeable glucose levels as well as fatty acid breakdown, produced in largely in adipose tissue, in humans, but also in muscle, and even in the brain) to a high CVD risk [29,30], together with IL-6, and IL-18 (Interleukin-18 is a protein (a pro-inflammatory cytokine) which in humans is encoded by the IL18 gene) [31,32]. When skeletal muscles exercise, they discharge a 100 times IL-6, with a related discharge of IL-10 and IL-1 receptor adversary [33,34], serving as powerful immune modulators that interfere with the encountered inflammation that illustrates obesity [5].

Uterine programming of glucose metabolism

Sheep models have been used to evaluate uterine programming of glucose metabolism, principally when maximum fetal growth is achieved in the offspring of these animal subjects. The study established that if the fetus was malnourished from the start, there was no noteworthy change in insulin sensitivity or glucose tolerance. Pregnancy has reduced GLUT4 expression, suggesting that the metabolic changes are tissue specific. According to Ford et al. [35], from early stage to midge station in sheep there is augmented body weight, fat deposition and glucose deregulation compared to its adolescent counterparts, with thrifty phenotype and accumulated data on fetal deficiency in relation to the beginning of diabetes mellitus, connected with an increase in the adipogenesis signaling cascade before the beginning of obesity [35].

Glucose metabolism and onset of obesity

Nutritional and hormonal factors can interfere with the proper development of the hypothalamus and its subsequent function, manifested by eating disorders [36,37]. Women with type 1 or 2 diabetes before pregnancy have a higher risk of motherly and fetal complications than patients with gestational diabetes especially because the glucose in the 1st trimester is teratogenic and can therefore lead to malformations. "Fuel-induced teratogenesis." is a theory that has been established to elucidate the teratogenic capability of glucose. Freinkel et al. [38] have proposed that fuel in the form of hyperglycemia is the cause of diabetic embryopathy and fetopathy associated with excess fuel. Various clinical discoveries have sustained this theory, particularly in some indigenous people including the Pima Indians [39,40] and Pacific Islanders [41,42] which have the maximum prevalence of gestational diabetes effects of glucose, and macrosomia. Overnutrition is known to enhance the physiological and epigenetic resulting in chronic hyperglycemia, hyperinsulinemia and hyperleptinaemia [43]. Fuel-induced cases are associated with motherly obesity and/or diabetes giving a specific metabolic profile: motherly hyperglycemia, hyperinsulinemia and low-grade inflammation. Meanwhile insulin cannot cross the placental barrier; glucose is the main secretagogue in the fetal pancreas around week 27 of gestation. The development of skeletal muscles is crucial for adulthood because it is liable for the majority of the oxidation rates of glucose and fats [44,45]. Macrosomal newborns have visceromegaly and large quantities of fatty tissue, but inadequate growth of skeletal muscle, exclusively type II fibers which are answerable for energy production/aerobic muscle. In a fuel-inducing environment, there is a divergence between myogenesis and adipogenesis, with chronic inflammation being the culprit for its switching undifferentiated via inhibition of AMPK, the downregulation of the pathways [45,46].

Developed diets inducing body weight loss

Several types of nourishments have been developed focusing on determining a favorable macronutrient composition in order to accomplish certain metabolic conditions which induce body weight loss [45]. For example, dietary recommendations involved diets low in fat, moderate in protein, and relatively high in carbohydrate,

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based on the fact that high-fat diets lead to less satiety [47] and a diminution in fat ingesting in the body, these nourishments meaningfully abridged the risk of cardiovascular disease by reducing circulating lipids [48]. Nevertheless, an opposing phenomenon has been detected; people following this nourishment began to upsurge weight instead of losing it, predominantly in Western Countries [49]. In response to the lack of efficiency of these nourishing recommendations, new substitute dietary regimes have been developed. The nourishments developed by Dr. Atkins, have extensively promoted carbohydrate content, with a low glycemic index and high fiber content [50]. These regimes induce:

a. speedy body weight loss enlarged satiety [51]

b. an associated reduction in cardiovascular disease,

c. the risk of diabetes [52].

However, only a few long-term and sufficiently randomized studies recommend this type of nourishment [53,54]. During the last decade, numerous studies have been realized to analyze the effect of high protein nutrition on weight loss, establishing a reduction in body weight with a higher maintenance of this weight loss [55,56]. Are these nourishments able to conserve a long-term weight loss? Studies on the physiological effects of these nourishments composition in the human population have been revealed to be convoluted due to lack of nourishment compliance as well as accurate reporting, that is why several animal models have been developed to control the properties of the nourishment on metabolism and afford the main information on this topic [5].

Central role of AMPK in controlling energy balance

AMPK plays a dominant role in the regulatory of energy balance, as a sensor of cellular energy quantum [57]. Therefore, the following question is expressed: What are the effects of nutritional ingredients on the activity of AMPK and lipids? Even though the exact mechanism connected to this phenomenon remains unknown, there is noteworthy evidence that high-fat nourishment is a risk factor that promotes:

a. obesity development,

b. glucose homeostasis modifications,

c. and cardiovascular system syndromes [58].

The main metabolic expressions of this diet are:

i. an upsurge in free fatty acids,

ii. diminished intracellular fatty acid oxidation,

iii. and an amassing of lipids on organs targeted by insulin [59].

A high fat nourishment is related with diminished expression of mRNA for the isoform AMPK-α2 as well as phosphorylation of AMPK, resulting in diminished action of this enzyme in the body, exactly in skeletal muscle, resulting in reduced absorption of glucose, however in adipose tissue, it promotes preadipocyte differentiation, lipolysis and adipocyte secretion (TNFα), propagating the method [60,61]. AMPK has a crucial role in the hypothalamus' nourishment ingestion control tower, constituting the signaling pathway for numerous hormones like leptin to normalize satiety. High fat nourishment induces hyperleptinaemia which is related with both peripheral and central resistance to leptin [62]. Abridged hypothalamic levels of leptin action may be due, at least in part, to the constitutive modification in the signaling pathway of AMPK. In the paraventricular nucleus of mice with diet-induced obesity, AMPK activity is constitutively diminished, and in the arcuate and medial nucleus of the hypothalamus leptin miscarries to overpower the action of AMPK [63].

Constituents controlling energy balance

Many ingredients can control energy balance.

a. Long-chain fatty acid esters are capable to obstruct AMPK kinase (AMPKK) and accordingly downregulate the signaling cascade of AMPK pathway [64].

b. Eicosapentanoic Acid (EPA) and Docosahexaenoic Acid (DHA) exert prophylactic properties in cardiovascular disease, protect against insulin resistance and obesity in mice with high-fat nourishments, and enhanced insulin response in human being.

c. The intake of polyunsaturated fatty acids has been shown to reduce the insulin resistance caused by high levels of saturated fats [65,66].

d. Ingestion of nourishments rich in Polyunsaturated Fatty Acids (PUFAs) has revealed to destroy hepatic lipogenesis, lower TAG-rich lipoproteins synthesis in the liver,

e. increase fatty acid oxidation,

f. and induction of genes that regulate fatty acid oxidation.

g. in skeletal muscle PUFAs increase thermogenesis, fatty acid oxidation, and glucose uptake [67,68].

All these proceedings are controlled by the action of AMPK. The mechanism by which PUFA may activate AMPK remains to be clarified, but numerous hypotheses have been projected such as:

i. an upsurge in the AMP/ATP ratio,

ii. diminished dephosphorylating of AMPK by regulator over the action of protein phosphatase 2A (PP2A),

iii. or enhanced AMPK activity secondary to raised plasma amounts of adiponectin, IL-6, leptin and others [69,70].

iv. The Clade creases the expression of AMPK-α2 and satiety and consequently declines body weight [71].

v. short-chain fatty acids synthetized by fermentation of carbohydrates in the intestinal lumen could be absorbed and upset hepatic glucose metabolism [72].

vi. The control of hepatic AMPK action could play a hazardous role in this process; nevertheless there is tiny data accessible on the effect of short-chain fatty acids on the action of AMPK.

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vii. In hepatocytes culture, acetate activates AMPK activity probably by growing the rate AMP/ATP [73,74].

viii. Butyrate supplementation can avoid the upsurge of insulin resistance in mice by encouraging energy expenditure through the induction of mitochondrial function, carbohydrates and AMPK. The harmful effect of high-carbohydrate nourishment on health is well identified [75].

Role of foods glycemic index in the management of obesity

There is presently much interest in the probable role of foods glycemic index in the management of obesity and other metabolic syndromes. It has been revealed that nourishments with low glycemic index may be advantageous in regulating body weight in two ways:

a. by oxidation, stimulating satiety

b. and secondly by increasing fatty acid

Both ways are explained by the action of AMPK [76]. However, a number of mechanisms that can be activated by the glycemic index of foods consumed in the diet may explain the changeability in the results of studies of weight loss via the glycemic index [77].

Adaptation of cells unable to sustain the energy demanding activities

Restriction of glucose causes stimulation of AMPK, which obstructs anabolic reactions that consume ATP, such as fatty acid, protein and cholesterol production pathways, and activation of catabolic reactions that engender ATP to maintain cellular energy deposits such as the oxidation of fatty acids and glucose [77]. AMPK regulates the myogenesis and differentiation of skeletal muscles and the differentiation of preadipocytes into mature adipocytes, via SIRT1 (NAD-Dependent Deacetylase Sirtuin-1 [silent mating type information Regulation 2 homolog1]) [78]. The loss of differentiation due to cellular malnutrition can be explained as a simple adaptation of a cell unable to support the energy-demanding activities that accompany differentiation. Nevertheless, there is an activated pathway in low-calorie cellular micro-environments, and it involves AMPK/Visfatina/SIRT1. Visfatin is a new adipocyte that exerts insulin-like actions [79]. The pathway is characterized by SIRT-mediated AMPK-dependent Viscata induction, resulting in a promotion of the NAD+NADH ratio, which induces the cessation of genetic transcription [80]. The advantageous activities of low-carbohydrate nourishment have been perceived in short-term trials, which justify the need for long-term studies to fully evaluate and fully recommend this type of nutritional recommendation [81]. Low-carbo-hydrate nourishments with high protein ingestion have become really widespread. The confirmation proposes that the foremost mechanism for its success is that high protein ingestion encourages weight loss by inducing thermogenesis and satiety [82,83]. Of course, it is not only the percentage of ingested protein but also the quality and amino acid quantity which regulates the loss-weight property [83,84]. Proteins exert their influence in different manners, from the intestinal lumen with activation of chemoreceptors which reply to amino acid/peptide attendance discharging Cholecystokinin (CCK), Glucagon-like Peptide-1 (GLP-1), or peptide YY to a higher central level, controlling neurotransmitter discharge in middle cellular levels regulating AMPK action [84,85]. A high-protein nourishment is capable of monitoring food intake due to enhanced POMC expression and repression of NPY in the hypothalamus, via activation of mTOR and low phosphorylation rates of AMPK [86,87]. Leucine affects AMPK pathway by obstructing it, and in doing so, it triggers the mTOR signaling pathway. Intraventricular injection of leucine in rats decreases food intake in a dose-dependent manner, and this influence is not perceived with other aminoacids. Though this is true, weight decrease, and food ingestion magnitude observe with the leucine treatment was similar to that realized by high-protein nourishment, which can clarify why leucine is the most abundant aminoacid in most of the protein-rich formulated nourishments [87]. The precise mechanism for leucine AMPK-inhibiting action is indefinite; nevertheless, it probably relates to allosteric activation of the Glutamate Dehydrogenase (GDH) consequential in raised substrate flux towards Krebs cycle, liberating AMP/ATP ratio, and reducing AMPK phosphorylation [88].

Alternative medicine has been a huge source of natural products now used in the treatment of obesity and insulin resistance, but the enormous majority of cases lack scientific confirmation that can warranty its usefulness and mechanism of action are usually unidentified. We wonder if the anti-diabetic plants frequently used in Cameroon can play as target for the management of childhood, adolescent and adult obesity [5].

Antidiabetic plants extracts or constituents important in the treatment of obesity

Momordica charantia Lin. (Cucurbitaceous) called Lepoho-kenan in Yemba (Fongo-Tongo district). The main phytochemical constituents of bitter melon that have reported hypoglycemic actions are:

a. cucurbitane-type triterpenoids charantin (a steroidal glycoside that is an equal mixture of stigmasterol glucoside and β-sitosterol glucoside), main constituent of the fruit

b. karaviloside IX,

c. momordicoside S and its aglycones momordicosides A, B, Q, R, and T.

d. polypeptide-p,

e. vicine,

f. ribosome-inactivating protein momordin [89].

Momordica charantia Lin. (bitter melon) is used in developing countries of Africa and Asia as an herbal medicine. It has increased prominence for its manifold hypoglycemic properties in animal models and humans. Polypeptide-p is a very operative hypoglycemic agent when administered subcutaneously [89] reported that curbitane triterpenoids (Mormodicoside S, and karavilosede XI) are capable to stimulate AMPK activity, weight loss, supporting

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GLUT4 translocation, and metabolic regulator. The Phytoalexin resveratrol (trans-revestrol) is naturally produced by bacteria or some fungi species. This polyphenol capable of enhancing AMPK, SIRT1, and Peroxisome proliferator activated-receptor gamma coactivator 1-α(PGC1-α), reducing Insulin-like growth factor 1 levels enhancing insulin sensitivity [90,91]. It has been revealed that *Momordica charantia* Lin. increases the effect of the AMP-Activated Proteinkinase (AMPK) pathway and decreases the expression of Phosphoenolpyruvate Carboxykinase (PEPCK) (Shih et al. 2014). Polypeptide-p is infrequently mentioned as "plant insulin," and it is one of the few of these active ingredients that have been studied in clinical trials. Berberine is an alkaloid isolated from *Momordica charantia* Lin. which acutely stimulates AMPK in myocytes and adipocytes, inducing GLUT4 translocation, weight loss, by lowering fat storage in adipose tissue even in pediatric population. This substance also decreases the differentiation rate of preadipocytes by phosphorylation [92,93]. In Cameroon, the decoction in water of fruit of *Momordica charantia* (200mg/kg) is taken three times daily to control both diabetes and obesity.

Gymnema sylvestre (Retz.) R.Br. ex Sm. (*Asclepiadaceae*)

Gymnema sylvestre can regulate numerous diseases associated to diabetes such as chronic inflammation, obesity, enzyme deficiencies and pancreatic β cell dysfunction. No other oral hypoglycemic herbal medicine currently exerts such a miscellaneous range of effects. *Gymnema sylvestre* root extract exhibited encouraging free radical scavenging action, with extreme inhibition of 81.3% [94]. Gymnemic acid an active constituent found in *Gymnema sylvestre*, has anti-obesity and anti-diabetic activities by reducing body weight and inhibiting glucose absorption. Several compounds isolated from Gymnema, avoid the accumulation of triglycerides in the muscle and liver and also reduce fatty acids accumulation in the circulation [95]. A recent clinical study has revealed that *Gymnema sylvestre* (Retz.) R.Br. ex Sm. extract has significantly reduced body weight, BMI and lower values for VLDL. Clinical approval and scientific validation are still mandatory before this use may be approved in the treatment of obese patients [95,96]. In Cameroon, the decoction in water of root bark of *Gymnema sylvestre* (200mg/kg) is taken three times a day to control both diabetes and obesity.

Coccinea grandis (L.) Voigt, syn. *Coccinia indica* Wight & Arn. (*Cucurbitaceae*)

Human trials have shown that the active components of a *Coccinea grandis* extract can reduce elevated levels of the enzymes glucose-6-phosphatase and lactase dehydrogenase in the glycolytic pathway, and restore lipoprotein lipase activity in the lipolytic pathway, with the control of hyperglycemia in diabetes [96]. In Cameroon, the decoction in water of leaves of *Coccinea grandis* (210mg/kg) is taken three times daily to control both diabetes and obesity.

Opuntia spp. *Opuntia engelmannii* Salm-Dyck ex Engelm. (*Cactaceae*)

Several species of the genus may contain Polysaccharide ODP-Ia that revealed antihyperglycemic effects through the protection of the liver from peroxidation damage and through the maintenance of tissue function, thereby improving the sensitivity of target cells to insulin. Recent study conducted on murine model suggested that *Opuntia vulgaris* syn. *Opuntia ficus-indica* treatment acts by inhibiting glucose absorption from the intestine and enhancing glucose uptake from insulin-sensitive muscle cells through the AMPK/p38 MAPK signaling pathway, capable to stimulate weight loss [96]. In Cameroon, the decoction in water of fruit of *Coccinea grandis* (80mg/kg) is taken three times daily to control both diabetes and obesity.

Panax ginseng C.A. Mey (*Araliaceae*) Ginseng

The proposed mechanism of the modulation of metabolic processes by ginsenosides is their activation of the Peroxisome Proliferator-Activated Receptors (PPARs) that regulate glucose and lipid metabolism, and the transcription of proteins involved in glucose and fatty-acid uptake. Recent studies have shown that ginsenosides activate AMPK pathway, resulting in suppression of hepatic gluconeogenesis and steatosis. Additional potential health effects of ginsenosides include anticarcinogenic, immunomodulatory, anti-inflammatory, anti-allergic, anti-atherosclerotic, antihypertensive, and antidiabetic effects, as well as effects on the central nervous system [96]. In Cameroon, the roots decoction of Panax ginseng (250mg/kg) is taken three times daily to control both diabetes and obesity.

Cinnamomum spp/ Cinnamon zeylanicum blume

A study on rat model of gestational diabetes showed hypoglycemic action of cinnamaldehyde by increasing insulin secretion and sensitivity through activating the antioxidant defense system, suppressing pro-inflammatory cytokines production and upregulating PPARγgene expression [96]. In Cameroon, the roots decoction of Cinnamon zeylanicum (200mg/kg) is taken three times daily to control both diabetes and obesity.

Allium. sativum L. (*Alliaceae*) Garlic

The higher insulin production is a result of the actions of allixin, S-allyl cysteine sulfoxide and diallyl trisulfide. Recent studies of S-allyl cysteine, the main organosulfur bioactive molecule in aged garlic extract, demonstrated its anti-diabetic, antioxidant, anti-inflammatory and neuroprotective properties. Studies in animal models and preliminary human studies have indicated beneficial effect of garlic and garlic extracts in the treatment of patients with diabetes and related metabolic disorders [96]. In Cameroon, the bulb decoction of *Allium sativum* (200mg/kg) is taken three times daily to control both diabetes and obesity.

Zingiber officinale Roscoe (*Zingiberaceae*)

Recent study reported improved insulin sensitivity and reduced total cholesterol and triglycerides as well as reduced C-reactive protein and prostaglandin E2 inpatients with type 2 diabetes. A double-blind, placebo-controlled, randomized clinical trial conducted on patients with type 2 diabetes who did not receive insulin showed that ginger supplementation significantly reduced serum triglyceride and reported a minor beneficial effect on serum

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glucose [96]. In Cameroon, the roots decoction of Zingiber officinale zeylanicum (200mg/kg) is taken three times daily to control both diabetes and obesity.

Achyranthes aspera var. pubescens (Moq.) C.C. Towns. (*Amaranthaceae*)

The Extract of *Achyranthes Aspera* (EAA) inhibited pancreatic amylase and lipase activity *in vitro* and elevations of plasma triacylglycerol level in mice. Furthermore, the antiobesity effect of EAA (900mg/kg) was assessed in mice fed a high-fat diet with or without EAA for 6 weeks. EAA significantly suppressed the increase in body weight, retroperitoneal adipose tissue, liver weights, and serum parameters, namely; total cholesterol, total triglyceride, and LDL-cholesterol level. The anti-obesity effects of EAA in high-fat-diet-treated mice may be partly mediated through delaying the intestinal absorption of dietary fat by inhibiting pancreatic amylase and lipase activity. *Achyranthes aspera* seeds are also reported to contain oleanene-type triterpenoid saponins. In our studies oleanene-type triterpenoid saponin was found to be 147.7µg/g of EEA along with 0.34mg/g of phenols and 0.30mg/g of flavonoids, which may be responsible for the anti-obesity activity. In conclusion, *Achyranthes aspera* seed may prevent obesity by reducing the excess accumulation of body fat and changing the serum lipid profile [97]. In Cameroon, the leaves decoction of *Achyranthes aspera* (140mg/kg) is taken three times daily to control both diabetes and obesity.

Costus maculatus Roscoe (*Costaceae*)

The effect of insulin at a concentration of 340nM and extract at 10µg/ml concentration was compared. It was shown that the extract produced about 96% glucose uptake compared to insulin in 3T3-L1 adipocytes. *Costus afer* considerably diminished plasma glucose after 30 to 60 minutes of oral absorption than the reference drug tolbutamide. *Costus afer* acts as an antidiabetic agent through biochemical mechanisms as well as restoration of pancreatic β-cell activity, enhancement of insulin resistance by sensitizing receptors, obstruction of liver gluconeogenesis, improved glucose absorption, and inhibition of G-6-Pase, α-amylase, and α-glucosidase activities. The stem and roots contain numerous bioactive constituents including diosgenin and aferosides A, B, and C named as the most expected constituents responsible for the antidiabetic activities of *Costus afer*. Diosgenin ameliorates insulin resistance by rising glucose usage and intracellular glycogen synthesis [98]. The administration of *Costus afer* extract induced a significant lowered serum TAG, TC, and LDL levels to near normal. Results from these studies reveal that *Costus afer* leaves might be explored in the managing of diabetes mellitus and its complications for example dyslipidemia [98,99]. In Cameroon water maceration of *Costus afer* leaves, rhizomes or stem is drunk at the rate of two glasses daily against diabetes and obesity.

Discussion

Control of food intake and pregnancy and mother and child postpartum follow-up

Excessive consumption of high energy meals should be avoided especially by pregnant women. It can facilitate macronomia/micronomia in newborns and lead to hyperglycemia/hypoinsulinemia in adulthood which is associated with changes in response to a new environment and changes in ovarian steroid hormone levels [8]. Hence, clinicians could focus on peri-conceptual interventions that prevent insulin sensitivity and insulin resistance, as well as the development of GDM predictive of early childhood growth regardless of birth weight. Pregnant mothers with GDM should be referred for lifestyle intervention as part of their postpartum follow-up care. Such an intervention could reduce the risk of recurrence of GDM with subsequent pregnancy and improve the life behaviors of mother and child. Interventions aimed at improving blood sugar control and increasing healthy behaviors during pregnancy may impact the development of overweight and obesity in offspring [7,8]. Healthy food and regular physical activity can prevent overweight and obesity. Overweight and obesity and associated non-communicable diseases can be largely prevented by:

a. limiting the consumption of foods with high energy density and high in fat and/or sugar (for example, sugary drinks, ultra-processed foods).

b. increasing the consumption of fruits and vegetables, legumes, whole grains and nuts.

c. practicing regular physical activity (30 minutes per day for adults) [8].

Make the healthiest choice, the easiest choice

According to the EGEA (European Garage Equipment Association), the high prevalence of obesity in the world; compels us to make our environment healthier to help everyone make the healthiest and most sustainable choices. The involvement of all sectors of society is decisive in changing our environments and making the healthiest choice the easiest in terms of accessibility, availability and price [100]. This challenge rests above all on political and societal choices in the fields of health, agriculture and education. According to the EGEA (European Garage Equipment Association), the high prevalence of obesity in the world; compels us to make our environment healthier to help everyone make the healthiest and most sustainable choices. The involvement of all sectors of society is decisive in changing our environments and making the healthiest choice the easiest in terms of accessibility, availability and price. This challenge rests above all on political and societal choices in the fields of health, agriculture and education [101].

Healthy nutrition and exercise habits

Treatment for obesity in adolescents focuses on developing healthy eating and exercise habits rather than losing a specific amount of weight. Reducing calorie intake and burning calories are two ways to achieve these goals.

a. Reduction of calorie intake

b. Establish a balanced diet with ordinary foods.

c. Make permanent changes in eating habits.

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d. Increased calorie burning.

e. Increased physical activity hosting summer camps for obese teens can help them lose weight, but if they don't continue the weight loss effort after the camp is over, the weight is usually regained. Tips to help teens cope with social issues, including low self-esteem, can be helpful.

f. Medication: Medicines that help reduce weight are generally not used during adolescence due to safety concerns. One exception is obese adolescents with a strong family history of type 2 diabetes. They are at risk of developing diabetes. The drug metformin, which is used to treat diabetes, can help them lose weight and also reduce their risk of developing diabetes [101,102].

g. WHO action

Adopted by the World Health Assembly in 2004 and reaffirmed in 2011 in a political declaration on No Communicable Diseases (NCDs), the Global Strategy on Diet, Physical Activity and Health outlines the actions needed to encourage people to eat healthy foods and exercise regularly. It calls on all parties concerned to take action at the global, regional and local levels to improve people's habits in terms of diet and physical activity. The 2030 Agenda for Sustainable Development recognizes that NCDs are a major obstacle to sustainable development. In this program, the Heads of State and Government committed to lead an ambitious national action by 2030 to reduce by one third, through prevention and treatment, premature mortality due to NCDs [103].

Significance and limitation of the used of antidiabetic plants against obesity

This work seeks to provide a comprehensive update on selected antidiabetic plants usually used in Cameroon, particularly on their extracts, phytochemical and dietetic constituents, pharmacological activities, and toxicological effects.

Protective ability against kidney damage

The presence of high proportions of micro and macronutrients such as carbohydrates, fats, proteins and various other active constituents in many herbal medicines, makes possible the opportunity of considering the corresponding plants as nutraceuticals. Evidence for the presence and abundance of phytochemicals in plants highlights the reasons why indigenous people use them. Organs like the liver and kidney must imperatively detoxify the body exposed to toxins or conventional and herbal drugs. The liver is frequently involved in the biotransformation of such substances to fewer toxic constituents via phase I and II reactions to increase their elimination by kidneys. In kidney impairment, its detoxifying capability is reduced. Toxicity of the kidney results in raised levels of sodium and potassium, in the serum and enlarged kidney. In cyclosporin-a-(Csa) induced nephrotoxicity animal model, there is commonly a substantial raise of serum K+,Na+,BUN and creatinine in negative control animals compared to the normal rats. In a gentamicin-induced nephrotoxicity model comprising oral intake aqueous *Costus afer* leaf extract, there was a significant decrease in sodium, blood urea level, and serum creatinine level. A perceived enhancement in tissue architecture with observable glomeruli and less cell inflammation occurred when *Costus afer* leaf extract with doses of 375-1125mg/kg was administered. This depicts the fact that *Costus afer* leaves have nephroprotective property [99].

Protective ability against heart damage

Intake of *Costus afer* leaf extract improved CCl4-induced cardiac toxicity. This was depicted by a noteworthy enhancement in the lipid profile as showed by low serum TAG, TC, and LDL levels to near normal [99].

Protective ability against liver damage

There was a significant decrease in serum AST and basic phosphatase (ALP) nearby to the normal at an oral intake of 400mg/kg of *Costus afer* extract likened to rat nourished with 200mg/kg of the extract. In a study model liver injury was induced by the oral administration of carbon tetrachloride (CCl_4) in rats. In another study, it was established that *Costus afer* stem extract possesses the capability to improve alcohol-induced liver damage in rats, signifying that *Costus afer* has pharmacological activity against alcohol liver cirrhosis [99].

Protective ability against testicle damage

Administration of aqueous leaf extract of *Costus afer* in rats with Pb-induced testicular damage was evaluated. The result showed irrelevant modifications in the weights of epididymis and testes when extract treated Pb group was compared with the normal control. The outcome according to the researchers demonstrates the fact that aqueous leaf extract of *Costus afer* may be protective against lead-induced testicular injury [99].

Protective ability against mitochondrial damage

Both *Costus afer* leaf and stem extracts obtained from diverse solvents remarkably inhibited Ca^{2+}-induced mitochondrial MPT when compared with an untreated mitochondrial fraction in the presence of Ca^{2+} ion. *Costus afer* hexane leaf extract at a dose of 10-60µg/ml meaningfully inhibited Ca^{2+}-induced MPT by 85.66% to 90.45% [46]. This suggests that *Costus afer* contain certain bioactive constituent that chelate calcium ion to help stabilize the membrane, thus blocking mitochondrial MPT. This demonstrates that *Costus afer* leaves could help treat and manage oxidative stress and neurodegenerative syndromes such as Alzheimer's disease [99]. Exogenous and plant toxic substances such as xenobiotic and molecules like colchicine found in *Gloriosa* spp, usually pose toxicity to some vital organs in the body even though these organs try to get elimination of the toxins. Many drugs are taken to cure and manage diseases and disorders and are seen to be effective at its purpose, but one cannot overlook its side effects [99].

Effects of *Costus afer*

The oral administration of aqueous *Costus afer* leaf extracts showed an important dose-dependent lessening of serum BUN and K+ [40]. Acute toxicity study was performed with hexane leaf extract on male rats which received orally 2000mg/kg of extract

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fraction after overnight fasting. The rats were observed for clinical signs including fur color, breathing rate, and death, after 24 hours. Yet, even at a dosage of 2000mg/kg bwt, no clinical sign of toxicity or death was observed, indicating that *Costus afer* leaf extract is nontoxic. However, a sub-chronic toxicity study demonstrated a significant reduction of Hemoglobin (HB) and total Red Blood Cell (RBC) count, signifying that long-term usage of aqueous leaf extract of *Costus afer* could provoke anemia. Additional investigation needs to be conducted to discover the bioactive constituents in the plant responsible for decreasing in Hb and total RBC count as well as the type of anemia triggered. It was also revealed that aqueous leaf extract of the plant generated an upsurge in weight of the liver and other clinical chemistry parameters such as ALT, ALP, AST, and TB. Histological study also revealed morphological and vacuolar changes in the hepatic cells which were concentration-dependent and more protuberant at a dose of 1125mg/kg. No damaging histological effect/deficiency on the kidney was detected [98,99]: *Achyranthes aspera* contains several important phytochemicals such as achyranthine, betaine, ecdysterone, hexatriacontane, pentatriaontane, 6-pentatriacontanone and tritriacontane. These constituents are responsible of numerous pharmacological activities such as anti-allergic, analgesic, antiparasitic, antipyretic, cardiovascular, hypoglyceamic and nephroprotective, spermicidal. Manifold folkloric uses such as antiperiodic, purgative and laxative, in a number of gastric complaints and in body pains. A toxicity research performed on *Achyranthes aspera* revealed that there was no abnormality observed in all animal groups after observations of changes in bodyweight, food and water intake as well as cage side. The entire plant powder methanol extract was shown to be nontoxic. Hence, this species is reasonably hopeful as a multipurpose and multi-constituents medicinal agent, consequently supplementary clinical trials should be achieved to corroborate its effectiveness [104]. Carried out with *Costus afer ker* aqueous extract, acute oral toxicity studies in male and female albnino Wistar mice, weighing between 28 and 35g, did not shown any sign of acute toxicity or death even at the dose of 4,000mg/kg. The experiment lasted for a period of 56 days. The overflowing cell volume, hemoglobin concentration, and the total red blood cell count diminished significantly ($p < 0.05$) in comparison with the control. Serum biochemistry showed no significant modifications in the activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase when compared with the control. The histopathological studies revealed no significant lesions in the heart, kidney, and liver. There were also no significant increase in weight between the experimental animals and the control [105].

A clinical trial revealed no confirmed reports of antagonistic reactions in humans accredited to Panax ginseng rhizome alone. Significantly, no consistent symptomology or findings have been accredited to, or acknowledged as being connected with, ginseng ingestion. Standardized ginseng extracts at a concentration of 4mg ginsenosides/100mg capsule and given at a dose of up to 114µg in senoside/kg have not resulted in unfortunate effects when administered to humans for periods of up to 12 weeks [106]. The oral administration of the *Coccinea grandis* at a dose of 0.75g/kg to rats for 30 days did not provoke adverse effects reflected in the normal condition, growth, body and relative weight of organs, clinical biochemical values, hematology and did not effect in histopathological irregularities. At some dose the extract was found to be safe [107]. A 52-week study of oral-repeated-dose at 0.01, 0.10 and 1.00% for the extraction powder diet of *Gymnema Sylvestre* (GS), was conducted in both female and male Wistar rats, along with a group fed exclusively with the basal powder diet without GS. No exposure-related modifications in body-weight, in the food intake, in the hematological inspections, or in the serum biochemical inspections were recognized. No histopathological alterations were perceived. Therefore, it was established that there was no toxic influence in rats treated with GS at up to 1.00% in the diet for 52 weeks, corresponding to 504mg/kg/day for male and 563mg/kg/day for female as mean daily intake [108]. A 21-day study of oral administration of 300 and 600mg/kg/24h of *Allium sativum* (garlic) bulb aqueous extract was investigated in both genders rats. The results showed that garlic extract proves toxic effects affecting weight growing, biologic parameters and histological organ structures [109]. Pregnant women must be warned about the use of plants such as *Costus afer* which have the tendency to induce abortion in the 3rd trimester. This result has lightened the inadequacy of information on the pharmacokinetics and pharmacodynamics of *Costus afer* extracts and its isolated constituents; accordingly, a call for more research in that regard is needed [105]. All these data reveals the need and opportunity of supplementary research in the development of new natural phyto-medicines for the management of obesity

Role play by antidiabetic plants in the metabolic and genetic control: a new way of regulating metabolic and cardiac diseases

Control of glucose and lipid metabolism by AMPK: AMPK controls the energy metabolism. It is a new therapeutic route to treat metabolic and heart diseases. To this end, AMPK intervenes in the control of:

a. The lipid metabolism by phosphorylating and inactivating ACC, a catalytic agent for the transformation of Acetyl-CoA in the liver and adipose tissue. Concretely, AMPK inactivates ACC and consequently inhibits the synthesis of fatty acids in lipogenic tissues.

b. The transcription of lipogenesis genes in the long term. AMPK performs this role by inhibiting the expression and activity of transcription factors such as: SREBPI (sterol regulatory element binding protein 1c) and ChREBP (carbohydrate response element binding protein) [110].

In addition, in the liver and the skeletal and myocardial muscles), the malonyl-CoA produced by ACC plays the role of a regulatory agent: in fact, it blocks the transport of fatty acids from the cytosol to the mitochondria by inhibiting Carnitine-Palmitoyl Transferase-1 (CPT-1). Therefore in these tissues, the activation of AMPK leads to a decrease of malonyl-CoA cytosolic concentration, thus facilitating the penetration of fatty acids into the mitochondria for their oxidation. By this mechanism, it was recently revealed that leptin and adiponectin, two adipokines secreted by adipose tissue,

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stimulate fatty acid oxidation in the liver and skeletal muscle, secondary to AMPK activation in these tissues [98,111]. Indeed, the accumulation of triglycerides in the liver and skeletal muscle participates in the pathophysiology of insulin resistance in humans and animals, while the lipid depletion of these tissues improves insulin sensitivity (concept of lipotoxicity). We can therefore see all the metabolic benefit that activation of AMPK and the reduction in lipotoxicity that accompanies it can have [111].

AMPK is correspondingly involved in the regulation of carbohydrate metabolism. Thus, activation of AMPK promotes insulin-independent glucose transport in skeletal muscle and the heart [112,113]. Once engaged in skeletal muscle, glucose is immediately oxidized rather than stored as glycogen, an energy-expensive reaction, via inhibition of glycogen synthase by AMPK. In cardiac muscle, AMPK stimulates glycolysis through a mechanism involving 6-phosphofructo-2 kinase (PFK-2) [114]. AMPK phosphorylates and activates PFK-2, leading to an increase in intracellular fructose-2,6-bisphosphate, a potent allosteric stimulator of PFK-1, a key enzyme in glycolysis. On the other hand, it has been demonstrated that the activation of hepatic AMPK by AICAR or adiponectin represses the expression of the main genes involved in gluconeogenesis, glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) and inhibits hepatic glucose production [115-117]. Indeed, a specific activation of AMPK in the liver, by reducing the expression of the key genes of neoglucogenesis, is sufficient to normalize the glycemia of ob/ob mice and of mice made diabetic by streptozotocin [115]. The current model of transcriptional regulation of gluconeogenesis genes by AMPK involves the inhibition of nuclear translocation of the transducer of regulated cyclic-AMP response element binding activator 2 (TORC2). With all of these data, one can logically imagine that pharmacological activation of AMPK could be a new therapeutic avenue in the management of insulin resistance and insulin-independent diabetes. The mechanisms of action of AMPK also partly explain the beneficial metabolic effects in humans of two families of anti-diabetics, biguanides (metformin and phenformin) and thiazolidinediones (rosiglitazone), which each activate AMPK [116-118].

Regulation of food intake: In addition to its role as a detector of the cellular energy state, AMPK could also be involved in the central control of satiety in the hypothalamus, a region of the brain playing a central role in the energy homeostasis of the organism by regulating food intake and energy expenditure. It has recently been shown that the activity of hypothalamic AMPK varies with nutritional status, AMPK being activated on an empty stomach and inhibited during satiety [119]. An interesting parallel has also been highlighted between the level of activity of hypothalamic AMPK and food intake in response to different hormones or metabolites known to be modulated by nutritional status: ghrelin and endocannabinoids activate AMPK and induce food intake while insulin, glucose and leptin act in opposite ways [120]. AMPK controls food intake, in particular via the expression of orexigenic. The demonstration of hyperphagia coupled with activation of hypothalamic AMPK in mice made diabetic by injection of streptozotocin [121] also confirms the idea that AMPK could constitute an interesting therapeutic target for the management of intake disorders.

Control of myocardial metabolism by AMPK: The heart must produce nearly 35kg of ATP daily to ensure its contractile activity and its role as a pump. It produces its energy from the oxidation of substrates such as fatty acids and glucose. Because of this, a continuous supply of oxygen is provided by the coronary arteries. The narrowing or occlusion of a coronary artery produces a decrease in myocardial perfusion (ischemia). Energy is produced from exogenous glucose but also from the breakdown of glycogen (glycogenolysis). Faced with this metabolic stress situation, glycolysis is stimulated, making it possible to provide a minimum of energy to maintain cell survival. AMPK plays a key role in this stimulation. On the one hand, activation of AMPK results in translocation of the glucose transporter GLUT-4 at the level of the plasma membrane, facilitating the penetration of glucose into the cardio-myocyte by an indirect and as yet unknown mechanism [113]. On the other hand, AMPK phosphorylates and activates PFK-2, leading to an increase in intracellular fructose-2,6-bisphosphate, a potent allosteric stimulator of PFK-1 [114]. In addition, energy-consuming anabolic pathways are inhibited during ischemia. Thus, protein synthesis (responsible for 30% of ATP consumption in basal metabolism) is reduced by phosphorylation and inhibition of the elongation factor eEF-2 by AMPK, making the elongation of peptide chains impossible. When myocardial perfusion is restored, oxidative metabolism is possible again and fatty acid oxidation becomes the main source of energy providing 80% to 90% of ATP production. The proposed molecular mechanism once again involves AMPK through its action on ACC, facilitating the penetration of fatty acids into the mitochondria and therefore their oxidation. It has in fact been shown that AMPK remains active during the first moments of reperfusion and that this causes inhibition of ACC, a decrease in the concentration of malonyl-CoA and therefore an increase in oxidation fatty acids [122].

Control of Metabolic Diseases by the Antiaging Gene Sirtuin 1 (Sirt 1)

Roles and definition of Antiaging gene Sirtiun 1 (Sirt 1)

Over nourishment in metabolic diseases is implicated in central nervous system dysregulation of neuropeptides with atypical peripheral hormonal signaling from the pancreas (insulin), adipose tissue (leptin and adiponectin) and gastrointestinal tract (neuropeptides) involved in chronic disease. Sirtiun 1 (Sirt 1) gene regulates food intake which controls life span and several chronic diseases including obesity and cardiovascular disease with effects on NAFLD, cognition, energy metabolism, inflammation, mitochondrial biogenesis, neurogenesis, glucose/cholesterol metabolism and amyloidosis. It is a class III nicotinamide adenine dinucleotide, which is a (NAD+) dependent histone deacetylase (HDAC) [123,124]. He plays the following important other roles:

i. it targets transcription factors to adapt gene expression to metabolic activity.

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ii. it is involved in the deacetylation of nuclear receptors with its critical implication in insulin resistance.

iii. Sirt 1 (Sirt 1) provides reparation of telomerase reverse transcriptase and genomic DNA restoration.

iv. it preserves the telomeres which maintain the stability of chromosomes and cell multiplying.

v. Sirt1 (Sirt 1) is indispensable for neurogenesis and calorie restriction activates Sirt1 with effects on longevity by modulating phosphoinositide 3 kinase pathways and cardiovascular alterations associated with age.

vi. Using Sirtiun 1, tissue nuclear receptors undergo apoptosis of histone and non-histone targets. This antiage gene targets transcription factors coactivator gamma receptor activated by peroxisome proliferators (PGC-1 alpha), p53, receptor x pregnane (PXR) to adapt gene expression to metabolic action, insulin resistance and inflammation.

vii. Sirt 1 is implicated to glucose regulation with the participation of Forkhead box protein O1 (FOXO1) apoptosis that include p53 transcriptional dysregulation and Peroxisome Proliferator Activated Receptor (PPAR) gamma nuclear receptor.

viii. Sirt 1-mediated regulation of other antiaging genes implicates apoptosis of p53 and FOXO which has produced importance in relation to autonomic illness of the brain and liver.

ix. Sirt 1 is implicated in mitochondria maintenance and transcriptional factor FOXO3a apoptosis that activate the non-amyloidogenic α-secretase processing of the amyloid precursor protein and reduction of amyloid beta (Aβ) generation in neurons.

x. Over nourishment is related with the suppression of Sirt 1 and other antiaging genes such as Klotho, p66Shc longevity protein) and FOXO1/FOXO3a (connected to autonomous of brain and liver illnesses.

xi. The Suprachiasmatic Nucleus (SCN) is provoked by Sirt 1 suppression and IGF-1 dysregulation involved in automatic cell death applicable to various chronic diseases including obesity, diabetes, Alzheimer's disease (AD) and Parkinson's Disease (PD).

xii. Sirt 1 is also involved with hepatic cholesterol regulation with effects on liver nuclear receptors involved with cholesterol flux and metabolism.

xiii. Sirt 1 is indispensable for caffeine metabolism with Sirt 1 regulation of cytochrome A1 (CYP 1A1) and cytochrome A1 (CYP 1A2) crucial for caffeine and xenobiotic clearance.

xiv. Sirt 1 Brain-Derived Neurotrophic Factor Regulation (BDNF) has been demonstrated with caffeine connected to Sirt 1/BDNF regulation and synaptic plasticity. Caffeine induces the transport of FOXO1 to the nucleus with significance for neuronal apoptosis and neurodegeneration in diabetes.

xv. 15-the regulation of Sirt 1 is related to the nutritional therapy which includes caffeine intake, and it is indispensable for primary hepatic caffeine metabolism which determines secondary hepatic glucose clearance, fatty acids, bile acids, xenobiotics and beta-amyloid which are closely linked to many long-lasting diseases for instance NAFLD, cardiovascular disease, diabetes, stroke and neurodegenerative disorders.

xvi. Caffeine is essential for the avoidance of blood brain barrier disruption but with NAFLD, excessive transport of caffeine to the brain is connected with neurodegeneration. Coffee may contain ochratoxin A which is a powerful neurotoxin applicable to mitochondrial apoptosis and which supersedes Sirt's regulation of mitochondrial biogenesis related to neurodegeneration [123-125].

Sirtiun 1 (Sirt 1) gene and caffeine metabolism with significance to NAFLD, diabetes and chronic diseases

Mitochondrial function has been reported to be important for chronic diseases with Sirt 1/p53 defects critical for mitophagy with significance for NAFLD, cardiovascular disease, obesity and neurodegenerative diseases. In the usual obesity/diabetes epidemic, caffeine metabolism may be imperfect, and the effects of caffeine are via mitochondrial biogenesis controlled by Sirt 1/p53 with doses of caffeine related to the p53-mediated mitophagy relevant to programmed cell death. Sirt 1 is significant for mitophagy in myocardial infarction and hepatic caffeine metabolism is now important for endothelial death and interference from endothelial Nitric Oxide (NO) synthase. The interests of nutritional therapy to prevent NAFLD and diabetes now include low-calorie nourishments that identify a single defective anti-aging gene in the development of diabetes. The gene defect includes the antiaging gene Sirtuin 1 (Sirt 1) which controls appetite, nuclear-mitochondria interaction, adipose tissue-liver crosstalk, synaptic plasticity, and proliferation of neurons in numerous populations of the body developing and developed world. Sirt 1 is important for the function of the Suprachiasmatic Nucleus (SCN) which preserves the synchrony between neurons which is essential for circadian rhythm and glucose clearance in the brain and periphery. Defective hepatic caffeine metabolism and the induction of T3DM have now become important for chronic diseases worldwide. Unhealthy foods and transcriptional dysregulation of Sirt 1 gene include inoperative cytochrome p450 enzymes with defective caffeine associated with defective glucose, fatty acid, cholesterol and beta-amyloid metabolism and induction of diabetes type 3. In chronic worldwide diseases the influence of defective caffeine metabolism effects cellular magnesium/calcum levels with magnesium deficiency (Sirt 1 activator) relevant to the induction of diabetes type 3 and numerous chronic illnesses [125].

Inhibition of Sirtiun 1 (Sirt 1) gene determine food intake dysregulation, insulin resistance and neurodegenerative disorders

Increased susceptibility to chronic disease, in developing countries is associated with urbanization and augmented access to food, epigenetic and immune system alterations. Down regulation of anti-aging genes decreases hepatic xenobiotic metabolism and may stimulate Multiple Organ Dysfunction Syndrome (MODS). For example Sirtiun 1 inhibitor like bacterial Lipopolysaccharides (LPS) destroys the expression of this gene with effects on neuropeptides

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such as brain-derived neurotrophic factor, neuropeptide Y and IGF-1 which are involved in the regulation of appetite (food intake) in the brain and in the periphery. LPS interrupts the hepatic metabolism of glucose, lipoproteins and cholesterol. LPS is involved in the homeostasis of cellular zinc with the importance of zinc for the maintenance of Sirt 1 activity and the function of hormones such as insulin and adipokines (adiponectin, leptin) involved in the regulation of appetite in the hypothalamus. In general toxic compounds are involved in the dysfunction of nuclear receptors such as the nuclear receptor Sirtuin 1 (Sirt 1) which determines the survival of humans and various species in relation to the toxicity to mitochondria in neurons and cells in peripheral tissues. But the role of diets/nutrients that control the absorption of bacterial LPS is essential in preventing NAFLD and neurological degeneration and the repression of antiaging genes may be related to LPS with the acceleration of dysregulation of appetite and chronic diseases. Sirtuin 1 inhibitors when consumed may inactivate Sirtuin 1/AMPK activation with unfavorable events associated with insulin resistance, obesity, and cardiac pathologies such as cardiac ischemia, related complications and diabetes [123]. Sirt is very importance because it can cancel the effects of other antiaging genes such as Klotho, p66Shc (longevity protein) and Fork head box proteins (FOXO1/FOXO3a). In Klotho adipose tissue gene expression profiles, p66Shc (longevity protein) of telomere length may be canceled by increased xenobiotics with shortening of telomere length [123-125].

Conclusion

In term of this work it important to proclaim that many over-the-counter dietary supplements which still have unsatisfactory medical information and scientific confirmation to support them are used in the management of obesity patients and connected metabolic disorders. In majority of the herbal medicines and secondary metabolites used in treating obesity, the mechanisms of action involve lifestyle modification, aimed at decreasing calorie intake, increasing energy expenditure and weight loss, remains the keystone of management of obesity. Diabetes management mechanisms such as regulation of insulin signaling pathways, translocation of GLUT-4 receptor and/or activation the PPARg as well as anti-inflammatory and immunomodulatory action could help in the treatment of obesity. Meanwhile, its efficiency is recurrently incomplete by significant weight regain in the lasting. *Opuntia* vulgaris treatment acts by inhibiting glucose absorption from the intestine and enhancing glucose uptake from insulin-sensitive muscle cells through the AMPK/p38 MAPK signaling pathway capable to stimulate weight loss. With its intestinal absorption inhibitor extract, an anti-obesity compound, *Achyranthes aspera* seed prevent obesity by reducing the excess accumulation of body fat and changing the serum lipid profile. Accordingly, successful management of obesity may require additional measures and adjunct pharmacotherapy seems to be progressively operational in this regard.

Furthermore, given the escalating worldwide epidemic of overweight and obesity, a standard alteration in our current approach to handling obesity may questionably be required, with more thoughtfulness being paid to the role long-term herbal therapy, associated to an enzyme involved in energy metabolism, to achieve and maintain recommended weight loss. Nutrition and environmental xenobiotics are now implicated in the defeat of antiaging genes with epigenetic modifications linked to the global epidemic of chronic disease. This study demonstrates that a favorable metabolic effects caused by the action of adipokines, leptin and adiponectin, or pharmacological constituents, depend on the activation of Sirtiun 1 genes and AMPK. Thus, due to its multiple tissue actions on energy metabolism, Sirtiun 1 gene and AMPK appears to be a therapeutic target of choice for the management of metabolic diseases such as diabetes, insulin resistance, obesity, and cardiac pathologies such as cardiac ischemia, related complications and diabetes.

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