1. Introduction

1.1. Obesity

Obesity, a latin word derived from *Obesitas* (*Ob* - over; *Esus* - Eating) means fat, stout, or plump. The World Health Organization (WHO) defines it as accumulation of extra fat that damage health and is generally defined through body mass index (BMI) of $\geq 30\ \mathrm{kg/m^2}$. BMI is a common index of weight/height and is represented by a person's weight in kilograms divided by the square of his/her height in meters ($\mathrm{kg/m^2}$) [1-3].

Obesity is the single largest risk factor for non-communicable diseases (NCD) such as cardio-vascular complications, cancer, diabetes mellitus, etc and these diseases account for more than 2/3rd of early deaths worldwide. It significantly reduces life expectancy (by 5-20 years), which in turn depends upon the severity of the condition and presence or absence of other co-morbid disorders [2, 4-7]. In addition to physiological complications, obesity leads to depression which is another major cause of exaggeration of associated illness, mental distress, unemployment and social distancing. In view of its multidimensional impacts, organizations such as World Obesity Federation, American and Canadian Medical Associations declared obesity as a chronic progressive disease instead of just considering a risk factor for other diseases [4, 8].

For the WHO, reduction in the obesity-related health burden as well as reversing the increased prevalence of obesity remains a high priority, including the target to halt obesity prevalence at the level it was in the year 2010 (target of the 'Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020'). In the declaration of the high-level meeting of the UN General Assembly on the prevention and control of non-communicable diseases of 2011, the importance of reducing unhealthy diet and physical inactivity was emphasized [8,9].

Energy imbalance between calories consumed and calories expended is considered as one of the fundamental causes of obesity and most of the current health recommendations rely on this fact. However, weight-loss interventions at the individual level, with the aim of reduced calorie intake and increased energy expenditure are not generally successful in the long term. At the first glance though, the individuals behavioural change (i.e., change in the activity patterns and diet) are more likely to get triggered as a result of the societal and environmental alterations [10]. Such behavioural changes might be ineffective in the absence of supportive policies especially in the sectors such as agriculture, food processing, health, transport, urban planning, marketing, education and others [11]. Hence, the WHO has acknowledged that increasing the

physical activity and healthy eating in the entire population must be guided through policies and real-time actions in the societies [4].

1.1.1. Global Epidemiology of Obesity

In the last few decades, obesity cases have increased around the world to pandemic magnitudes. As per a recent study on worldwide BMI trends based on measured body weight and height data of 128.9 million children and adults, obesity prevalence has been found to increase in every single country since 1975 [11]. An accelerated increase in BMI has been observed in South Asia (India, Bangladesh, Pakistan, Bhutan and Nepal), Southeast Asia (Malaysia, Indonesia, Philippines, Thailand, Sri Lanka and Vietnam), the Caribbean (Cuba, Belize, Jamaica, Dominican Republic and Puerto Rico) and Southern Latin America (Brazil, Argentina, Paraguay, Uruguay and Chile). The prevalence of a BMI $\geq$ 30 kg/m² significantly varies by country and ranges from 3.7% in Japan to 38.2% in the United States [5,11] (Figure 1.1). Other than for Asia and parts of sub-Saharan Africa, more people with obesity than with underweight are there throughout the world. Between the years 1975 and 2014, the obesity (BMI $\geq$ 30 kg/m²) prevalence increased from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women. In 2014, 0.64% of men and 1.6% of women were having exposure to morbid obesity (BMI $\geq$40 kg/m²). The trends during the same period for adults (Figure 1.2) indicated that variation in BMI ranged from virtually no change in North Korea, countries in sub-Saharan Africa and Nauru, to an increase (>6%) in several other parts of the world during the same time. Obesity prevalence and BMI dynamics are widely varied across the countries for the steepness of increases, slowing-down and/or periods of acceleration. Remarkably, the rate of BMI increase has been sluggish after 2000 in high-income and a few middle-income countries than the rates in the previous century for both, children and adults. It might be too early to confirm if this reflects changes in society or is an active response to this growing health concern [5,11].

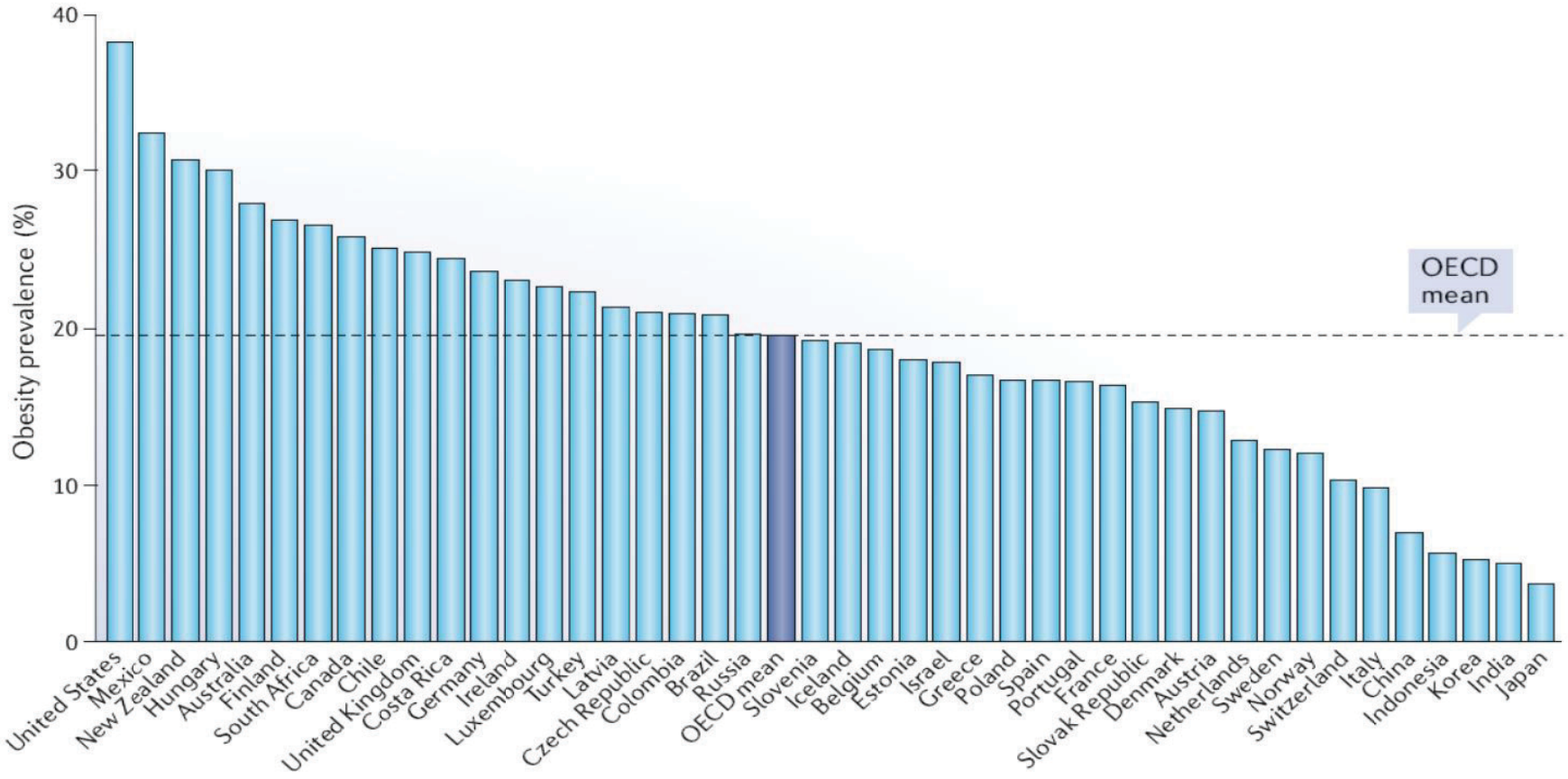
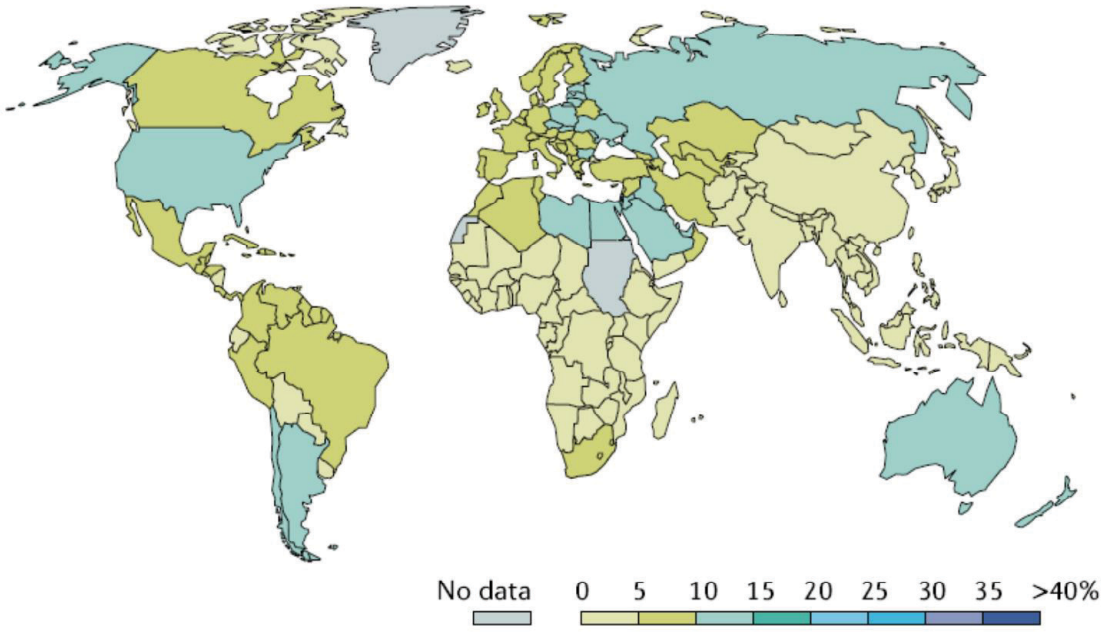


Figure 1.1. Prevalence of obesity (BMI $\geq$30 kg/m^2) in selected countries from Organisation for Economic Cooperation and Development, OECD 2017, adapted from [11].

A]



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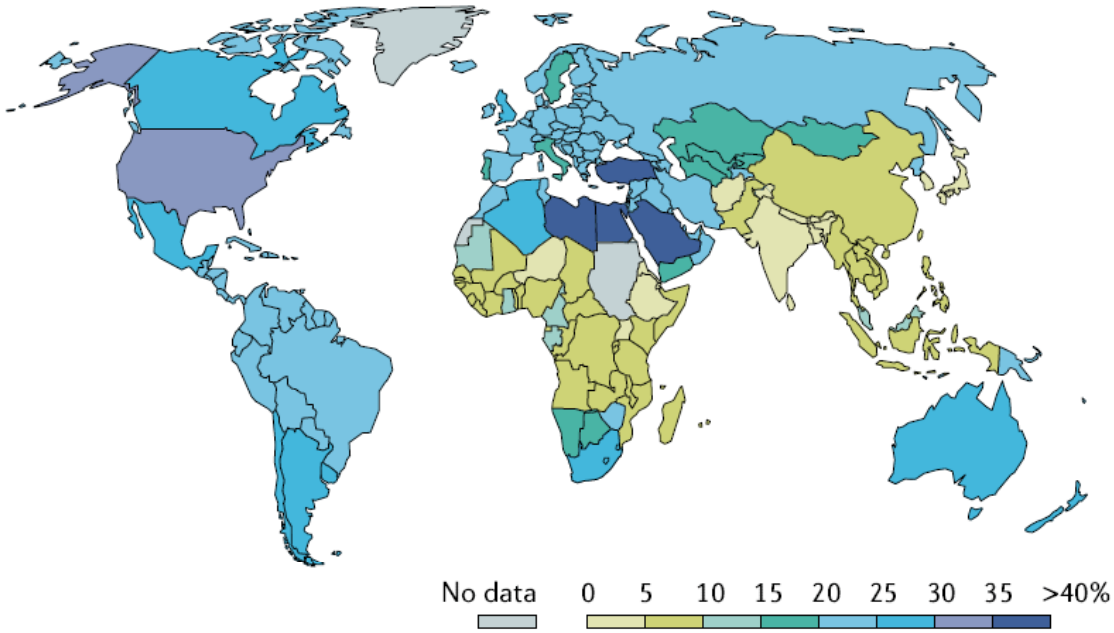

Figure 1.2. Percentage of adults defined as obese by country in 1975 (Part A) and 2014 (Part B). {Data from the WHO, Global Health Observatory, adapted from [5]}.

1.1.2. Types of Obesity

Obesity is classified under two major classes, based on fat distribution, as central (android) and peripheral (gynoid). Central obesity is characterized by fat depots around the abdomen (abdominal obesity), while peripheral obesity is characterized by fat depots around the hips and thighs (pear-shaped obesity) [5,6].

A different classification indicated by the National Health Service (UK), classified obese individuals under six categories and is based on a study conducted by the University of Sheffield in the UK and the Harvard School of Public Health in the US [7]. The study included data from 4000 obese adults and reported six clusters. These were: (i) healthy young females; (ii) heavy-drinking males; (iii) anxious middle-aged; (iv) healthy and affluent elderly; (v) physically sick and happy elderly (vi) poorest health. On the basis of BMI, an individual with BMI between 25-29.9 kg/m^2 is considered overweight, while a BMI greater than 30 kg/m^2 is obese. Summary of BMI based classification for overweight and obesity in different age groups are presented in Table 1.1. Similarly, for children aged between 5-19 years or under 5 years, overweight and obesity are determined using the respective WHO Growth Reference Medians [8-11].

Table 1.1. Summary of BMI based classification for overweight and obesity in different age groups.

	Adults (>19 years)	**Children (5-19 years)**	**Children (< 5 years)**
Overweight	25-29.9 kg/m^2	BMI-for-age >1 standard deviation above WHO Growth Reference Median	BMI-for-age >2 standard deviations above WHO Growth Reference Median
Obese	30-34.9 kg/m^2 (Class I) 35-39.9 kg/m^2 (Class II) ≥ 40 kg/m^2 (Class III)	BMI-for-age >2 standard deviations above WHO Growth Reference Median	BMI-for-age >3 standard deviations above WHO Growth Reference Median

However, consistent shreds of evidence have indicated that not only BMI is highly specific, but also has low/moderate sensitivity in determining an individual as overweight or obese. For instance, literature reports suggest that around 50% of all adults with excessive body fat were categorized as non-obese according to BMI. Similarly, at least 25-50% of children/adolescents having excess body fat were categorized as having a healthy BMI-for-age [11]. Waist-Hip Ratio (WHR) is the other parameter used to determine obesity and is considered more accurate in

comparison to BMI. The WHO STEP wise approach to Surveillance (STEPS) provides a standardized procedure for measuring waist and hip circumference, which states that "The measurement of the circumference of waist must be made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest" and "The measurement of the hip conference must be made at the widest portion of the buttocks". Further, the tightness of the tape and the subject posture is to be maintained as suggested in the STEPS protocol. A WHR greater than 0.85 for women and 1.00 for men is considered obese [10,11].

1.1.3. Causes and Comorbidities

At least 9 factors have been identified that contribute to obesity, and includes (i) type of food; (ii) reduction in physical activity; (iii) sleep deprivation; (iv) consumption of drugs; (v) endocrine disruptors; (vi) infections; (vii) ethnicity; (viii) age; and (ix) intrauterine effects [12]. A vast majority of obesity has been observed with the food type and reduced physical activity, while other factors share a minor role in the global obesity epidemic [12,13]. Multiple factors, *i.e.,* over-eating, physical inactivity and low energy expenditure (Table 1.2) can impact the chronic positive energy balance, thus causing obesity. Weight gain can be a result of a combination of reduced energy expenditure, increased energy intake, and low physical activity [14]. In particular, these comorbid risks are known to be observed with people with central obesity, while peripheral obesity was found to be protective [14-16].

Table 1.2. List of factors influencing the chronic positive energy balance [14-16].

Over-eating	Low energy expenditure	Physical inactivity
Social/cultural	Ageing	Social/cultural
Lack of knowledge	Sex	Physical challenges
Peer pressure	Genetics and epigenetics	Chronic fatigue
Uncontrolled eating	Neuroendocrine factors	Muscle pain
Hunger	Prandial thermogenesis	Joint pain
Emotional eating	Brown fat	Low fitness level
Snacking	Sarcopenia	Emotional barriers
Lack of sleep	Microbiota	Workplace
Medications	Medications	Medications

1.1.4. Treatment of obesity

The current guidelines by the 'American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS)' recommend a loss of a minimum of 500 kcal per day, through diet modification and physical activity to achieve significant weight loss.

However, a negative response to only lifestyle modification might necessitate the use of other adjunctive strategies such as bariatric surgery and/or anti-obesity pharmacotherapy to achieve significant weight loss [16,17].

During the last century or so, many drugs were approved for the treatment of this silent killer disease, however, most of these drugs were withdrawn due to severe side effects reported during post-marketing surveillance. Generally, the drugs approved by the US Food and Drug Administration (FDA) for obesity are intended to be used for patients with a BMI of ≥ 30 (obese) or ≥ 27 (overweight) with an associated risk factor, e.g., diabetes and/or hypertension. All the medications are specified as aides to increased physical activity, caloric restriction and behavioural modifications.

Examples of FDA approved drugs for the treatment of obesity include orlistat (Xenical), a fixed-dose combination of immediate-release phentermine and extended-release topiramate (Qsymia), a fixed-dose combination of bupropion and naltrexone (Contrave), and Liraglutide (Victoza). Cetilistat has been approved for the treatment of obesity with complications, by the Japanese Ministry of Health, Family and Welfare on September 20, 2013, and has completed phase III clinical trial [18]. However, the drug has not been approved by the US FDA to date.

As making diet and lifestyle changes can be a daunting task, many people look towards dietary supplements endorsed for weight loss in the anticipation that these products will help them to achieve their weight-loss goals more easily. The dietary supplements for weight loss include a wide variety of products and are available in many different dosage forms including but not limited to capsules, liquids, tablets, bars and powders [12]. These products are marketed with numerous claims, including that these products reduce macronutrient absorption, appetite, body fat, weight, increase metabolism and thermogenesis. Weight-loss products may contain at least dozens of ingredients, and many at times, the total number of ingredients could be more than 90 [12]. Common ingredients in these supplements include botanicals (herbs and other plant components), dietary fiber, caffeine, and minerals. Table 1.3 provides a comprehensive view of such botanicals used as a treatment for obesity. It also provides details of the part of the botanicals used, family to which it belongs, major natural products (constituents) and plausible mechanism of action. Overall, 50+ different families of the various medicinal botanicals, have shown anti-obesity potential. The families such as Solanaceae, Zingiberaceae, Celastraceae, Magnoliaceae and Theaceae contribute a large number of anti-obesity agents. The natural products from the botanicals belonging to these families have many different types of mechanisms for anti-obesity action. The recommended approach in the quest to explore more

efficient treatment could be using either multiple products or products having multiple mechanisms of action. In general, botanicals and their natural products with potential action in the treatment of obesity help to regulate body metabolism, dissolve the fat accumulated in the body, act as a general body cleanser, help to eliminate the craving for food, reduce water retention, stimulate glandular secretions and help in removing constipation. However, on the other side, in a report on dietary supplements for weight loss, the U.S. Government Accountability Office has said that, "little is known about whether weight loss supplements are effective, but some supplements have been associated with the potential for physical harm" [17,19]. Many weight-loss supplements are costly, and some of these products' ingredients can interact or interfere with certain medications [20].

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity.

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Root of *Platycodon grandiflorum*	Campanulaceae	Platycodins	Increase lipid metabolism	[21]
Root of *Radix platycodi*			Lipolysis in fat cells and Pancreatic lipase inhibition	[22]
Rhizome of *Curcuma longa*	Zingiberaceae	Curcumin	Lowering of the lipid Increased activity of hepatic acyl-CoA oxidase	[23]
			Lowering of the body fat and weight gain through anti-angiogenic activity	[24]
			Slowing down of adipogenesis in 3T3-L1 cells and alteration of expression of AP2 (a marker of adipocyte maturation) messenger ribonucleic acid (mRNA)	[25]
Rhizome of *Alpinia officinarum*		3-Methylethergalangin,5-hydroxy-7-(49-hydroxy-39- methoxyphenyl)-1-*p*-henyl-3-heptanone	Inhibition of pancreatic lipase	[26]
			Reducing triacylglycerol, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and action on leptin levels and alanine aminotransferase (ALT)	[27]
Rhizome of *Zingiber officinale*		Gingerol, Paradol, Shagol	Enhances lipid profile	[28]
Tubers of *Dioscorea species* like *D. deltoidea*, *D. prazeri D. floribunda* and *D. composite*	Dioscoreaceae	Dioscin, diosgenin	Inhibition of pancreatic lipase	[29]
Leaves of *Salix matsudana*	Salicaceae	Apigenin-7-O-β-D-glucoside	Reduction of plasma triglycerol levels and hepatic total cholesterol content	[30]

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity ……*Continued*

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Fruit rind of *Garcinia cambogia*	Clusiaceae	Hydroxycitric acid (HCA)	Affects the release and availability of 5-hydroxytryptamine, 5-HT (responsible for controlling appetite)	[31]
Fruits of *Garcinia gummi-gutta* or *Garcinia cambogia*			Regulation of lipid biosynthesis	[32]
Whole plant of *Clusia nemroisa*		Betulinic acid	Significant reduction in total cholesterol, blood glucose and elevation of hormones like insulin and leptin; reduction in activity if amylase and lipase	[33]
Whole plant of *Acanthopanax senticosus*	Araliaceae	Acanthopanaxoside E, silphioside F, copteroside B	Reduces low-density lipoprotein (LDL)-Cholesterol and triglycerides levels (TGs)	[34]
Fruits of *Acanthopanax senticosus*			Inhibition of pancreatic lipase	[35]
Rhizome of *Panax japonicas*		Chikusetsusaponins	Inhibition of pancreatic lipase activity and regulation of body weight	[36]
Roots and berries of *Panax ginseng*		Protopanaxadiol, protopanaxatriol	Regulation of body weight through the reduction of food intake	[37]
Whole plant of *Panax ginseng*		Saponins	Inhibits energy gain, regulates hypothalamic neuropeptides and serum	[38]
Leaves of *Acanthopanax sessiliflorus*			Inhibition of pancreatic lipase	[39]
Stems and leaves of *Panax quinquefolium*			Decreases levels of triglycerides in plasma and increased levels in faecal matter, probably due to inhibition of pancreatic lipase	[40]

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity ……*Continued*

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Flowers of *Gardenia jasminoide*, *Crocus sativus*	Rubiaceae Iridaceae	Crocin	Decreasing the absorption of cholesterol and fat through inhibition of pancreatic lipase	[41]
Fruit of *Gardenia jasminoides*	Rubiaceae	Crocetin and crocin	Inhibiting activity of pancreatic lipase	[42]
Beans or seeds of *Coffea arabica*		Polyphenols	Increased energy expenditure, increased mRNA levels of acetyl CoA carboxylase-1 & 2- stearoyl – CoA desaturase-1, pyruvate dehydrogenase kinase, etc.	[43]
Leaves of *Salvia officinalis*	Lamiaceae	Carnosic acid and carnosol	Reduction of TGs. Reduced weight gain and reduction in epididymal fat weight	[44]
Leaves of *Rosmarinus officinalis*		Carnosic acid	Inhibition of 3T3-L1 adipocyte differentiation accomplished by blockade of mitotic clonal expression, Blocking of PPARγ & FABP4 expression	[45]
Leaves and leaf buds of *Camellia sinensis*	Theaceae	Polyphenols - (-)-Epigallocatechin 3-O-gallate (EGCG)	Inhibiting activity of pancreatic lipase	[46]
			Lipolysis inhibitory activity	[47]
Leaves of *Nelumbo nucifera*	Nymphaeceae	Phenolic compounds	Accelerates the lipid metabolism through the expression of Uncoupling protein 3 (UCP3)	[48]
Seeds of black soya bean	Leguminoseae	Polyphenolic pigments	Effects cell growth, cell differentiation and lipolysis in 3T3-L1 cells, inhibits proliferation of pre confluent pre adipocytes & maturing post confluent adipocytes	[49]

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity ……*Continued*

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Roots and stems of *Salacia reticulata*	Celastraceae	Mangiferin, (-)-epicatechin, (-)-epigallocatechin	Regulates high fat diet induced body weight gain through controlling white adipose tissue (WAT)	[50]
			Reduces body weight and mesenteric fat accumulation, increase adiponectin levels in plasma, improves abdominal glucose metabolism, enhance lipogenesis genes, suppress intracellular triacylglycerol accumulation, and suppress lipolysis genes through activation of 5' AMP-activated protein kinase-α (AMPKα) in adipocyte	[51]
			Inhibition of differentiation of adipocytes maturation or the expression of metabolic genes & proteins like peroxisome proliferator-activated receptor-γ (PPARγ), affects binding protein (C/EBP)α, glyceraldehyde 3 phosphate dehydrogenase (GPDH),	[52]
Leaves of *Catha edulis*		Cathinone	Reducing the feeling of hunger	[53]
Root of *Actinidia arguta*	Actinidiaceae	Ursolic acid	Not clear, might be due to enhancement of lipolysis and inhibition of pancreatic lipase	[54]
Beans of *Phaseolus vulgaris*	Fabaceae	Phytohemagglutinin	Reducing appetite through modulation of cholecystokinin and glucagon peptides, inhibition of alpha amylase	[55]
Roots of *Glycyrrhiza glabra*		Glycyrrhizin (GLZ)	Reduces plasma TG, activates phosphorylation of AMPK	[56]
		Flavonoids	PPAR mediated pathway	[57]

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity ……..*Continued*

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Dried powder of *Rhizoma coptidis*	Ranunculaceae	Berberine	Lowering of degradation of dietary polysaccharides, body and visceral adipose lipid levels and blood sugar levels	[58]
Leaves of *Ginkgo biloba*	Ginkgoaceae	Terpene trilactones, including ginkgolides and bilobalide	Activity through inhibiting pancreatic lipase	[59]
Fruits of *Evodiae fructus* or *E. rutaecarpa*	Rutaceae	Evodiamine, Rutecarpine	mRNA mediated weight reduction	[60]
Fruits of *Citrus depressa Hayata*		Flavonoids	Decreases the body weight gain, reduce white adipose tissue, reduces the plasma triglycerides/leptin levels, lowers the mRNA levels of lipogenesis-related genes, *viz*., acetyl-CoA-carboxylase 1, activating protein 2, fatty acid transport protein, stearoyl-CoA desaturase 1, and diacylglycerol acyltransferase 1	[61]
Fruits of *Capsicum spp*	Solanaceae	Capsaicin	Regulates appetite by acting on ghrelin, glucagon-like peptide 1 (GLP-1) and peptide YY	[62]
			Up-regulation of proteins responsible of lipid metabolism including of UCP2 and UCP3	[63]
Fruits and leaves of *Morus austrails poir* (mulberry)	Moraceae	Rutin, resveratrol anthocyanin and deoxynojirimycin	Reduces body weight gain, reduce fasting plasma glucose levels, decrease plasma triglycerides, liver lipid peroxidation levels and adipocyte size	[64]

Table 1.3. Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity ……..*Continued*

Part/ Botanicals	Family	Natural Products	Plausible mechanism of action	Ref.
Leaves of *Cudrania tricuspidata*		Anthocyanins – polyphenolic pigments	Reducing body weight and plasma triglyceride levels through inhibition of pancreatic lipase	[65]
Leaves of *Wasabia japonica matsum*	Brassicaceae	-	Reduces body weight and epididymal WAT by alteration in genes, enhanced PPARα expression, suppression of sterol regulatory element-binding proteins (SREBP-1C) expression	[66]
			Lowering of liver weight, enhanced levels of adiponectin and PPARα, supressing SREBP-1C; In WAT- supressed expression of leptin PPARγ & C/EBPα	[67]
Seeds of *Aesculus turbinata*	Sapindaceae	Saponons – escins, desacylescins, deacetylescins. Escins Ib and IIb, deacetylescins Ib and IIb with the angeloyl moiety	Inhibiting activity of pancreatic lipase	[68]
Pericarps of *Sapindus rarak*		Triterpene oligoglycosides, saponin - rarasaponins I and II, and raraoside A		[69]
Brown algae of *Eisenia bicyclis*	Lessoniaceae	Phlorotannins	Inhibiting activity of pancreatic lipase	[70]
Onion peel extract (OPE)	Liliaceae	Quercetin (QCN)	Suppressing pre-adipocyte differentiation and inhibiting the process of adipogenesis	[71]

Different mechanisms of action through which the majority of botanicals based anti-obesity drugs work are depicted in Figure 1.3. Lowering of the plasma lipid levels is the most commonly occurring mechanism of action. The next most common mechanism observed amongst the anti-obesity drugs was inhibition of pancreatic lipase and it was shown by more than 30 botanicals and their natural products [72]. As an example, the plants from Solanaceae family exert anti-obesity activity by inducing anorexia, inhibiting pancreatic lipase, reducing the accumulation of white adipose tissue, regulating gene expression, *viz.,* inhibiting ghrelin and increasing PPAR-α and PPAR-β expression, etc.

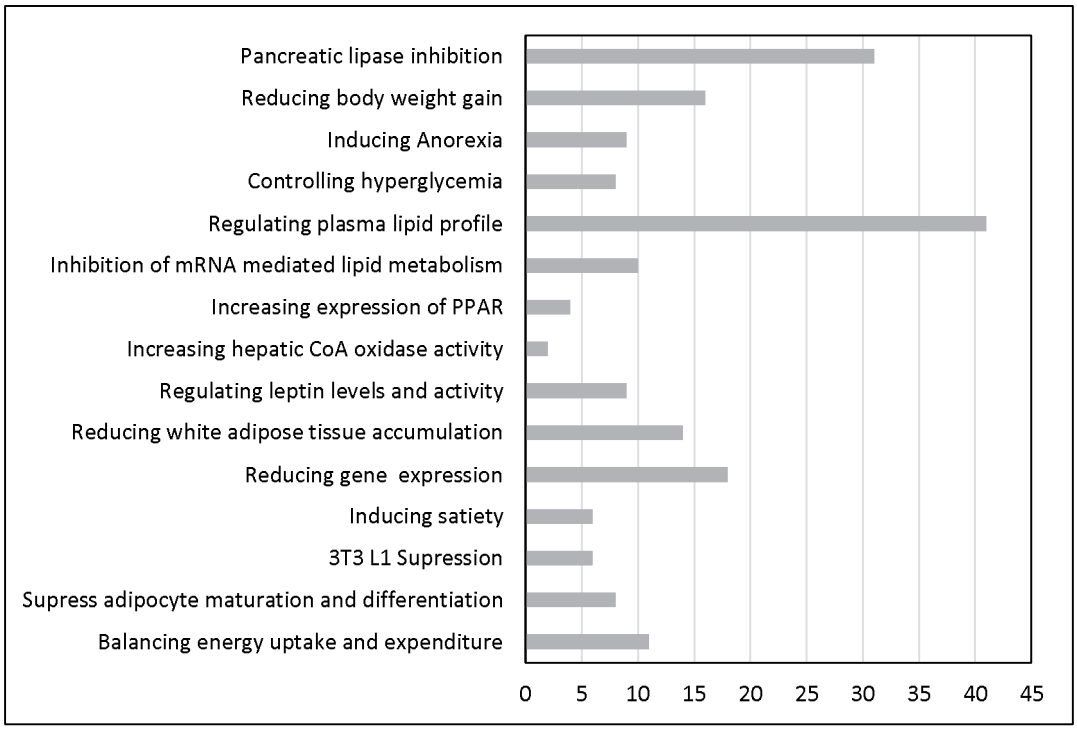

Figure 1.3. Various categories of mechanisms of action of anti-obesity activity by botanicals and their natural products {Adapted from Karri *et al.* [72]}

Figure 1.4 shows the distribution of anti-obesity activity amongst different parts of the botanicals. It is clear that the leaves of different botanicals possess a supreme therapeutic perspective against obesity, followed by fruits, roots, seeds, etc.

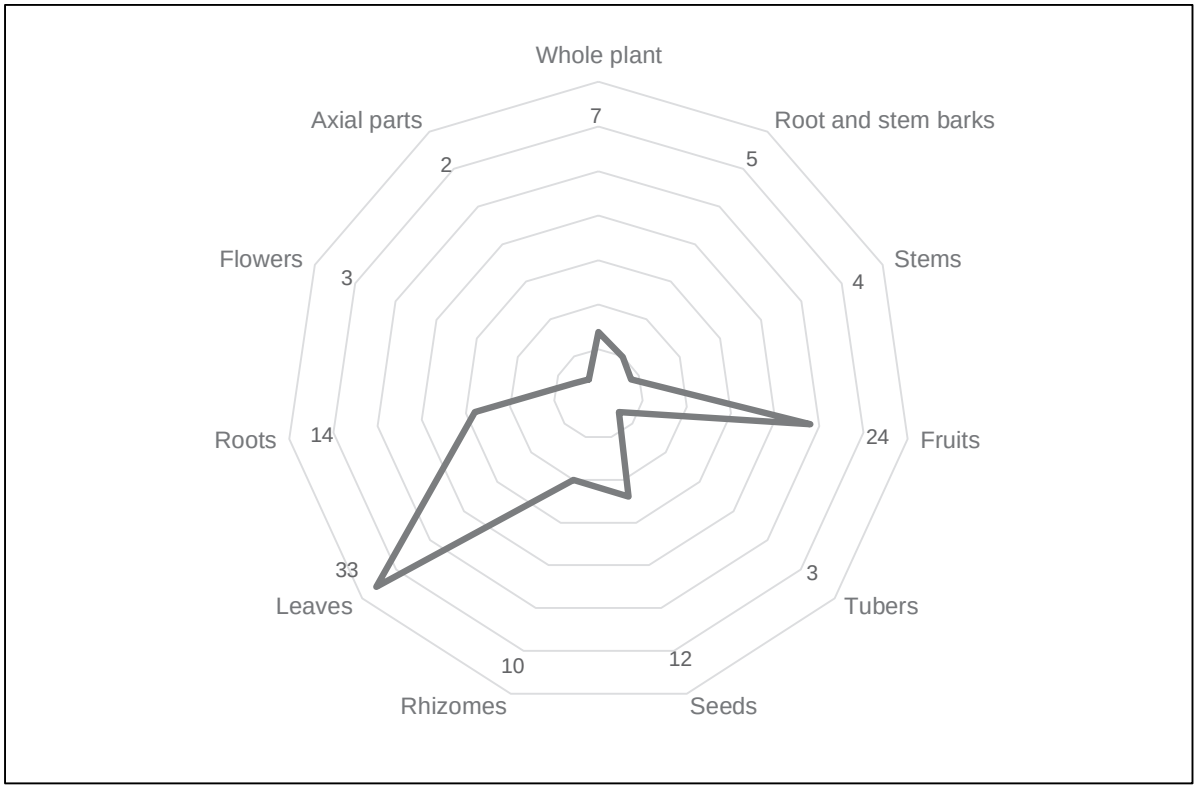

Figure 1.4. Radar chart depicting the distribution of anti-obesity activity in various botanical parts.

While a lot of information is available on the part of the botanicals responsible for anti-obesity activity, very little research has focused on understanding the molecular level mechanisms behind the activity [72]. The other challenges with botanicals include the lack of availability of the uniform quality of the material and problems with the identification of bioactive components through sensitive bio-assays and target identification. A growing threat of obesity to global health would encourage researchers and scientists to put intense efforts into finding an efficient mechanism of action at the molecular level from natural products

The distribution of different chemical classes from which the majority of anti-obesity natural products belong are shown.in Figure 1.5. The data suggests that the flavonoids play a major role in controlling the body weight followed by polyphenolic compounds and many others [72].

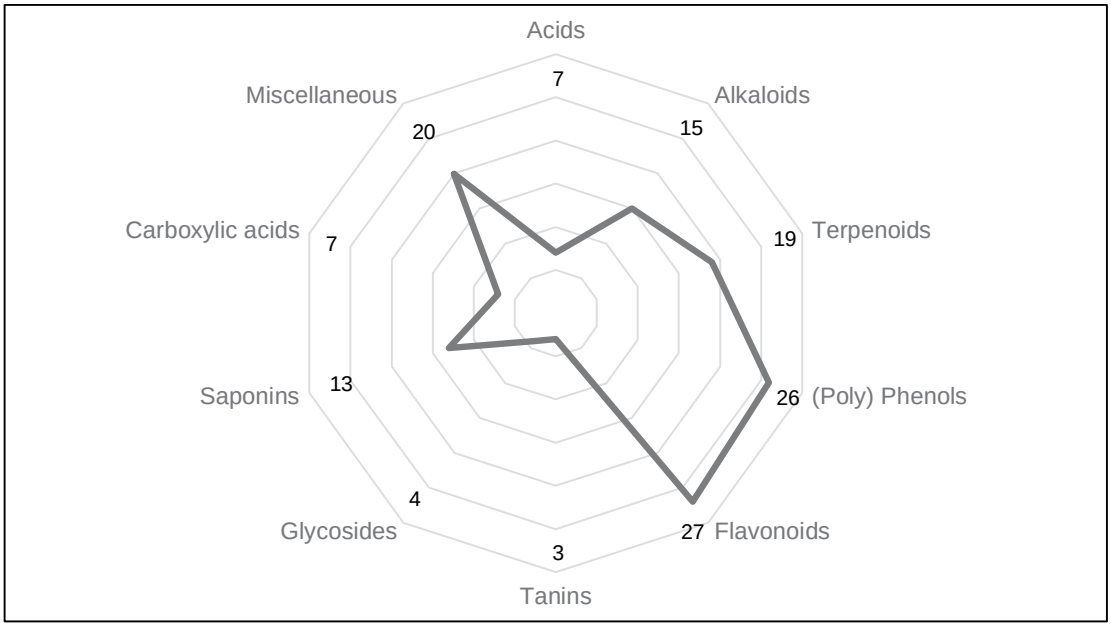

Figure 1.5. Chemical categories of natural products responsible for the anti-obesity activity.

1.2. Pharmacokinetics

Pharmacokinetics (PK) is defined as what the body does to a xenobiotic. It includes the study of absorption, distribution, metabolism and excretion (ADME) of compound or drugs after its administration. Any new chemical entity (NCE) cannot be a drug unless it has favourable safety and efficacy properties [73]. The concentration of the NCE in the systemic circulation is determined through PK properties. Approximately 40 % of NCE fail due to poor PK properties [74]. There are numerous *in vitro*-and *in vivo* PK studies usually conducted as a part of the drug discovery process. The absorption of a compounds is influenced by the solubility/dissolution of compounds in the gastric media as well as the permeability through the gastrointestinal barrier. Several *in vitro* assays are planned to understand the permeability characteristic of a compound. It includes the pH dependant solubility in different gastric fluids, aqueous solubility, log P, everted gut study, permeability using cell lines and *in situ* absorption [75-76]. These assays are used to explore the absorption behaviour of a compound. A large number of NCEs face the issue of low solubility which becomes the rate-limiting step that affects bioavailability [77]. The distribution of the drug in the body is crucial to reach the target sites. After reaching systemic circulation free drug partitions into different tissues. If the volume of distribution (V_d) of the drug is higher than the total body water then it has high partitioning to tissues e.g, cationic amphiphilic drugs (hydroxychloroquine) partition in the lysosomes leading to very high V_d. Conversely, if V_d is lower than the total body water then the drug has high protein binding [78-79].

Along with absorption and distribution, metabolism also plays an important role in PK. The liver is the most significant organ for the metabolism of drugs [80]. The metabolism process converts the lipophilic drug to hydrophilic moiety so that it gets excreted out of the body. The metabolism of xenobiotics may lead to the formation of active/toxic metabolites. The *in vitro* metabolic stability in the liver microsomes, S9 fractions, cytosol, hepatocytes and recombinant cytochrome enzymes (CYP) can explore the metabolic fate of a drug. *In vivo* metabolite identification and quantification provide vital information about the drug metabolism [81]. Metabolism affects the elimination half-life of the drug. CYP inhibition studies are used to assess the potential of possible drug-drug interactions or herb-drug interaction [82-83]. Phase-II metabolism such as glucuronidation, sulfation, and other conjugation reactions are also responsible for the metabolism of xenobiotics [84]. The majority of drugs and metabolites are excreted primarily through urine, feces, milk, saliva and bile. The kidney is the primary organ responsible for the elimination of drugs. Renal excretion has three steps glomerular filtration, tubular secretion and re-absorption.

The various predication, extrapolation and modelling methods are available to predict the *in vivo* PK parameters. The single-dose, multiple-dose PK studies are also important to check CYP induction or inhibition due to repeated dose. The PK parameters like half-life ($t_{1/2}$), volume of distribution (V_d), clearance (Cl), mean residence time (MRT), area under curve (AUC), steady-state concentration (C_{ss}), time to reach maximum concentration (T_{max}), and maximum plasma concentration (C_{max}) defines the PK properties of a compound. Moreover, the PK parameters like half-life ($t_{1/2}$) are crucial in the deciding dosage regimen. To estimate the absolute bioavailability, the intravenous (*i.v.*) PK study is required. The AUC obtained in the *i.v.* study is used for the calculation of bioavailability [85]. The bioanalysis is usually carried out through high-performance liquid chromatography (HPLC) and ultra-pressure liquid chromatography coupled with mass spectrometry (UPLC-MS/MS).

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