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FLAVONOIDS IMPACT ON PREVENTION AND TREATMENT OF OBESITY AND RELATED METABOLIC RISK FACTORS

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ABSTRACT: Metabolic syndrome, the most prevailing health concern worldwide, and their incidences are increasing at a very high rate, resulting in enormous social costs. Obesity is a measure risk factor for non-communicable disease such as cardiovascular diseases, diabetes, cancer, and inflammation-based diseases. Therapeutic strategies for managing this syndrome include synthetic drugs and surgery, which entail high costs and serious complications. Over the last decade, there has been an increase in the interest for the expansion of anti-obesity drugs, with particular attention paid to those from natural sources. Flavonoids or bioflavonoids derived from the Latin word flavus, mean yellow, and are ubiquitous in plants; these compounds are the most abundant polyphenolic compounds in the human diet and have been found to possess many beneficial effects with advantages over chemical treatments. Several clinical and research studies has suggested that flavonoids have been investigated in great depth and have shown a wide range of anti-inflammatory, anti-oxidant, anti-microbial and anti-cancer properties. Beneficial effects of dietary flavonoids on glucose homeostasis for the prevention and treatment of obesity and diabetes support the various *in-vitro* cell and *in-vivo* animal studies. Furthermore, well designed clinical trials are still needed to focus on both safety and efficacy of these flavonoids. In this paper, we have to summarize the current progress of the anti-obesity potential of natural flavonoids and their various mechanisms that target multiple molecular for preventing the cluster of diseases.

INTRODUCTION: Obesity presents a major challenge to chronic disease prevention, long-term sedentary lifestyles, consume large amounts of fast food, or suffer from genetic disorders. Fueled by economic growth, industrialization, mechanized transport, urbanization and a nutritional transition to processed foods and high-calorie diets over the last 30 years, many countries have witnessed the prevalence of obesity in its citizens double, and even quadruple [1].

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Obesity is an independent risk factor for metabolic syndrome; major medical problems associated with the development of hypertension, type 2 diabetes, dyslipidemia, sleep apnea, respiratory disorders and ultimately life-threatening cardiovascular disease, stroke, and certain types of cancer [2, 3].

In children, it is now well established that higher body-mass index (BMI) values, even at levels far below current overweight classifications, are associated with increased risks of type 2 diabetes in adulthood [4]. Today, more than 60 % of Americans are overweight, and if the current trajectory continues, the rate will reach 86% by 2030. A recent finding from WHO shows more than 1.9 billion adults were overweight, and 650 million were obese adults worldwide in 2016. [5, 6, 7, 8]

According to the International Obesity Taskforce, more than 300 million categorized obese people who have a body mass index greater than 30 kg/m^2. India is the second most populous country in the world and is currently experiencing a rapid epidemiological transition in the form of industrialization and urbanization. Childhood obesity is one of the most serious global public health challenges of the 21st century, affecting every country in the world [9].

WHO has issued guidelines to support primary healthcare workers to identify and manage children who are overweight or obese. In just 40 years, the number of school-age children and adolescents with obesity has risen more than 10-fold, from 11 million to 124 million (2016 estimates). The condition also affects younger children, with over 38 million children aged under 5 living with overweight or obesity in 2017. [10, 11] One of three children born in the early current century is expected to develop obesity-related diabetes [12].

Obesity is largely preventable, and urgent action is needed to reduce exposure to their causal factors, such as unhealthy diet and physical inactivity. Real examples of measures through which policymakers can influence food systems to promote healthy diets and prevent malnutrition in all its forms, including undernourishment, stunting, wasting, micronutrient deficiencies, overweight, and obesity, as well as diet-related non-communicable diseases [13]. Consuming a healthy diet throughout the life-course helps prevent malnutrition in all its forms as well as a range of noncommunicable diseases and conditions. The exact make-up of a diversified, balanced, and healthy diet will vary depending on the individual needs, cultural context, locally available foods and dietary customs [14].

TABLE 1: NEW DEFINITION OF OBESITY FROM THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS

Diagnosis	Body mass index (BMI)	Clinical component (Complications) *
Overweight	25.0-29.9	No complications
Obesity Stage I	≥30	No complications
Obesity Stage I	≥25	One or more mild-to-moderate Complications
Obesity Stage I	≥25	One or more severe Complications

***** Type 2 diabetes, hypertension, cardiovascular disease, and Increase waist circumstance.

In 2016, the American Association of Clinical Endocrinologists released new diagnostic criteria of obesity based on BMI combined with obesity-related complications (see **Table 1**) [15]. The cases of child obesity in developing countries are increasing day by day, as compared to developed countries [16].

From a thermodynamic perspective, obesity is a result of the imbalance between energy intake and energy expenditure. Role of dietary fat intake in the increasing prevalence of obesity comes from studies examining the concurrent changes in obesity and fat intake over extended periods [17]. Epidemiological evidence for a relationship between fat intake and obesity was proved by a statistically significant relationship between energy-adjusted fat intake and one or more measures of obesity [18]. Energy intake is food intake; energy expenditure is derived from complex thermogenesis processes that include basal metabolism, adaptive thermogenesis, and physical activity. Adaptive thermogenesis refers to an increase in heat production through futile metabolic cycles in response to environmental or behavioral changes (excess food consumption, change in the composition of the diet, modification of ambient temperature, or a variety of pathogenic stimuli) [19].

While lifestyle modifications aimed at reducing calorie intake and increasing energy expenditure remain the cornerstone of obesity management. Reducing body weight by lifestyle alteration is advisable, but sometimes drug intervention is necessary [20]. The complex pathogenesis of obesity indicates the need for different intervention strategies to confront this problem with a simple drug therapy which is more acceptable to patients. The regulation of energy homeostasis for metabolic diseases is one of the most rapidly advancing topics in biomedical research today [21]. Breakthrough in understanding the molecular mechanisms regulating body weight have also provided potential opportunities for therapeutic intervention and has brought renewed hope and vitality for the development of anti-obesity drugs [22]. Although, a plethora of research data available on obesity, it remains, largely, an unsolved medical problem. The market for anti-obesity drugs is like a mushroom, as it accounts for 2-6% of total health care costs in several developed countries [23, 24].

Obesity drugs can be divided into five categories: central appetite suppressants, digestion and absorption blockers, metabolic promoters, obesity gene product inhibitors, and other drugs for the treatment of obesity. However, the burden of previous weight loss pharmacotherapy that has been withdrawn due to safety concerns underlines the need for caution and close follow-up of patients undergoing pharmacological interventions for obesity treatment (see **Table 2**) [25-30].

TABLE 2: CURRENT TREATMENT OF OBESITY

Class of Drugs	Examples
Centrally acting sympathomimetic agents	NE release / NE reuptake inhibitor: Phentermine, diethylpropion, phendimetrazine, desoxyephedrine. NE & 5HT reuptake inhibitor: Sibutramine
Serotonergic agents	Non selective: Fenfluramine, dexfenfluramine, Selective: Lorcaserin
CB1 receptor antagonist	rimonobant, taranabant, otenabant, surnibant, ibipinabant
Lipase inhibitors	Orlistat, cetilistat
Antidiabetic agents	GLP1 analogs: Exenetide, Liraglutide. Biguanide: Metformin. SGLT-2 Inhibitor: Sitagliptin, saxagliptine. DPP-IV Inibitor: Dapogliflozin. Islet amyloid peptide: Pramlinitide
Antidepressant agents	Bupropion
Anti-epileptic agents	Topiramate, zonisamide
Combination agents	Phentermine and topiramate, Naltrexone and bupropion
Experimental peptides	Leptin, peptide YY, oxyntomodulin, melanocortin 4 receptor agonist

Inadequate results after cessation the lifestyle modification or pharmacotherapy compelled the researchers and physicians to rethink to find a new, safe, and striking therapeutic alternative for this global health concern. Natural products have been in attention as an effective option to reduce body weight and body fat. A vast range of these natural products and medicinal plants, including crude extracts and isolated compounds from plants can be used for treating obesity and diabetes is not only a priority for developing safer alternatives to pharmaceuticals, which transitorily lower the body weight, blood glucose and prevent high cardiovascular disease morbidity, but also enhance the antioxidant system, insulin action, and secretion [31, 32]. Many scientific communities have become increasingly interested in the low-level chronic inflammation, oxidative stress, molecular regulation of triglyceride synthesis and fatty acid oxidation through the phytochemicals, presenting an exciting opportunity for the discovery of newer anti-obesity agents. Clinical findings of herbal plants are effective in the field of weight loss therapy, and animal experiments have begun to disclose the potential mechanisms of the various herbal medicine [33].

Anti-obesity mechanisms for herbal plants included a reduction in lipid absorption, reduced energy intake, increased energy expenditure, decreased pre-adipocyte differentiation and proliferation, or decreased lipogenesis and increased lipolysis (see **Table 3**) [34, 35, 36]. However, some combinations of medicinal plants may result in either lower efficacy or cause unexpected side-effects.

TABLE 3: VARIOUS MECHANISM OF ACTION OF NATURAL ANTI-OBESITY PLANTS IN HUMANS

Mode of Action	Natural Preparations
Inhibiting pancreatic lipase activity	Chitosan [37], Levan [38], Mate tea [39], Oolong tea [40], Jasmine tea [41], Green tea [42]
Enhancing thermogenesis	Seaweed [43], Bitter orange [44], Soybean [45]
Preventing adipocyte differentiation	Turmeric [46], Capsicum [47], Banana leaf [49], Brown algae [50], Garlic [51], Flaxseed [52], Black soybean [53]
Enhancing lipid metabolism	Herb teas [41], Cinnamon [54]
Decreasing appetite	Pine nut[55], Pomegranate leaf [56], Ginseng [57], *Hoodia gordonii* [58]

Emerging evidence, from both experimental and epidemiological studies, has shown that an antioxidant-rich diet could contribute to protection against free radical production and oxidative damage, induction of antioxidant signaling pathways, enhancement of the endogenous antioxidant defense system, attenuation of oxidative stress, with consequent prevention of obesity and related co-morbidities.

Flavonoids: Extensive investigations have been conducted to identify dietary components that may influence the accumulation of excess body fat. Among such components, flavonoid compounds

hold a key role [59]. Dietary flavonoids might be considered as anti-obesity agents since they can reduce adipose tissue mass, thereby decreasing intracellular free radical formation [60]. Flavonoids regulate carbohydrate digestion, adipose deposition, insulin release, and glucose uptake in insulin-responsive tissues through numerous cell-signaling pathways.

Recent studies provide growing evidence that polyphenols from plant foods, due to their biological properties, may be unique nutraceuticals and represent supplementary treatments for various aspects of metabolic syndrome. The various researcher reviews the scientific evidence for the hypothesis that dietary flavonoids prevent or attenuate obesity and another metabolic risk factor. Thousands of naturally occurring flavonoids have been reported in various plants; they show many beneficial effects with advantages over chemical treatments [61, 62]. Structurally, flavonoids are based upon a fifteen-carbon skeleton consisting of two benzene rings (A and B) linked *via* a heterocyclic pyrane ring (C). Flavonoids are classified into flavonols (*i.e.* quercetin, kaempferol, resveratrol and myricetin), flavanones (*i.e.* eriodictyol, hesperetin, naringenin and naringin), isoflavonoids (*i.e.* daidzein, genistein and glycitein), flavones (*i.e.* apigenin and luteolin), flavan-3-ols (*i.e.* catechins and epigallocatechin gallate) and anthocyanins (cyanidin) [63].

Flavonols are the subgroup of flavonoids most widely contained in vegetables, such as onions, leeks, brussels sprouts, kale, broccoli, tea, berries, beans, and apples. Flavonone compounds are found abundantly in citrus fruits. Isoflavones are highly concentrated in soybeans and soya products, as well as legumes. Good sources of flavones include celery, parsley, various herbs, and hot peppers. Flavanols are found in green and white teas, cocoa, grapes, apples, berries, fava beans, and red wine.

Anthocyanidins are abundant in red, purple and blueberries, pomegranates, plums, red wine as well as red and purple grapes [64, 65]. They have a putative role as antioxidants, showing beneficial effects on inflammatory processes, cardiovascular diseases, and other pathological conditions [66, 67]. For example, these compounds actively reduce plasma triglycerides by inhibiting the absorption of dietary lipids and possess inhibitory effects on digestive enzymes like trypsin, amylase, and lipase.

Flavonoids are of particular interest, owing to their preventive role against several human diseases, arising from their wide spectrum of biological actions, including anti-inflammatory, antioxidant, antiviral, anticancer and neuroprotective activities. Nowadays, major attention is being focused on the free radical scavenging and metal ion-chelating activity of these compounds. Of note, flavonoids can inhibit the enzymes responsible for superoxide production (*i.e.*, xanthine oxidase and protein kinase C) as well as cyclo-oxygenase, lipoxygenase, microsomal succinoxidase, NADH oxidase, and to exert also an inhibitory effect on the expression of iNOS, largely related to oxidative stress conditions. Numerous studies have demonstrated the potential health benefits of natural flavonoids against obesity and insulin resistance. Based on several *in-vitro* animal models and some human studies, flavonoids appear to play a role in many of the metabolic processes involved in obesity and related morbidity.

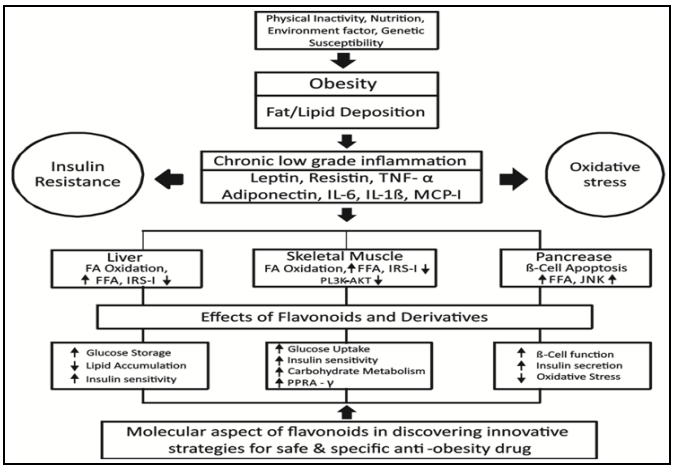

FIG. 1: DEVELOPING NEW STRATEGIES BASED ON MOLECULE ASPECT OF FLAVONOIDS AND SUBSEQUENT EFFECTS ON SKELETAL MUSCLE, LIVER, AND PANCREAS. TNF-α: tumor necrosis factor-alfa, IL-6: interleukin-6, IL-1β: interleukin 1beta, MCP-1: monocyte-chemo-attractant protein-1, FA: fatty acid, FFA: free fatty acid, IRS-1: insulin receptor substrate 1, PL3K: phosphatidylinositol 3-kinase –AKT: serine/threonine kinase, JNK: c-Jun N-terminal kinase, PPRA-γ: peroxisomal proliferator-activated receptor gamma.

Impact of Flavonoids on Obesity and Other Related Metabolic Risk Factor:

Obesity and Oxidative Stress: Oxidative stress is a process generated by an imbalance between the

production of reactive oxygen species (ROS) and antioxidant defense mechanisms. At low concentrations, ROS act as mediators regulating an array of physiological functions, a process designated as redox signaling. By contrast, at high concentrations ROS can lead to oxidation of biological macromolecules, such as proteins, lipids, carbohydrates, and nucleic acids, thus contributing to the pathogenesis of several chronic diseases. A growing body of evidence highlights the relevance of oxidative stress in obesity and related co-morbidities. The researcher observed the increased oxidative stress in accumulated fat as a key pathogenic mechanism of obesity in both human subjects and rodents[68]. Indeed, excess accumulation of visceral fat in the abdominal cavity has been associated with increased risks of metabolic dysfunction, diabetes, and CVD mortality [69, 70].

Several mechanisms have been proposed to explain the enhanced oxidative stress in the presence of obesity, including disorders of mitochondrial and peroxisomal fatty acid oxidation, hyper-consumption of O_2, and impairment of antioxidant defenses. Notably, the expression and activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, have been reported to be significantly reduced in the adipose tissue of obese individuals [71]. Obese humans and rodents the levels of oxidative stress-associated markers are elevated in plasma and urine samples. Studies suggested possible effects of flavonoids in counteracting obesity and related co-morbidities through a decrease in oxidative stress and related inflammatory conditions. In this situation nutritional stress, such as an excess of fat intake, promotes systemic oxidative stress, characterized by hyper-production of reactive oxygen species, leading to cellular alterations that include impaired energy metabolism, altered cell signaling, and cell cycle control, impaired cell transport mechanisms and overall dysfunctional biological activity [72].

Obesity and Inflammation: Interleukin 6, approximately 30% of which is produced by adipose tissue, not only predisposes to insulin resistance but enhances the hepatic production of acute phase proteins, such as C-reactive protein or fibrinogen. Various inflammatory mediators may directly contribute to atherosclerotic plaque progression and rupture. Therefore, inflammation within white adipose tissue may be a crucial step contributing to the emergence of many of the pathologic features that characterize the metabolic syndrome and result in diabetes and atherosclerosis.

Obesity and Insulin Resistance: Type 2 diabetes mellitus, the most common type of diabetes, is a long-term metabolic disorder characterized by impairments of both insulin secretion and action [73]. In obese individuals, adipose tissue releases increased amounts of NEFA (Non-esterified fatty acid), glycerol, hormones including leptin and adiponectin, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance. Insulin resistance generates compensatory hyperinsulinemia with over-stimulation of pancreatic β-cell function and induction of insulin receptor [74]. Insulin resistance is strongly associated with obesity, physical inactivity, and increased mass, especially in visceral or deep subcutaneous adipose depots leads to large adipocytes that are themselves resistant to the ability of insulin to suppress lipolysis. The free fatty acid can further decrease insulin sensitivity through inhibition of insulin-mediated glucose uptake transporters (*i.e.*, GLUT4) I in skeletal muscle and by contributing to hyperinsulinemia. Additionally, an elevated triglyceride level can cause pancreatic β-cell dysfunction, accelerated apoptosis, and hepatic gluconeogenesis [75].

Several circulating hormones, cytokines, and metabolic fuels, such as NEFAs originate in the adipocyte and modulate insulin action. Researchers proposed that increased NEFA delivery or decreased intracellular metabolism of fatty acids increases the intracellular content of fatty acid metabolites such as diacylglycerol, fatty acyl-coenzyme A, and ceramides. These metabolites activate a serine/threonine kinase cascade leading to serine/threonine phosphorylation of insulin receptor substrate-1 and insulin receptor substrate-2, and a reduced ability of these molecules to activate PI(3)K.

Therefore, downstream of events due to NEFAs diminished insulin-receptor signaling and impair β-cell function that insulin resistance. Researcher suggests based on several *in-vitro* animal models and some human studies; flavonoids appear to play

a role in many of the metabolic processes involved in type 2 diabetic mellitus. These studies provide a strong rationale for well-powered, randomized placebo-controlled intervention trials to be performed in patients with diabetic complications and given combination with current anti-diabetic drugs, as the action of flavonoids may be most effective as an adjunctive rather than a primary therapy Animal and cellular studies [53].

Obesity and Dyslipidemia: Imbalance in lipid metabolism seen due to abdominal fat accumulation has been well characterized and include hypertriglyceridemia, reduced HDL cholesterol, and increased numbers of small, dense LDL particles. The hypertriglyceridemia seen with abdominal obesity and insulin resistance is related to the over secretion of triglyceride-rich very low-density lipoprotein particles. Augmented rate of hepatic FFA uptake stimulates the secretion of apo B-100, leading to amplified numbers of apo B-containing particles and possibly hyper-triglyceridemia.

Obesity and Cardiovascular Disease: Obesity has long been known to be associated with increased development of CVD. Both increased BMI and waist circumference represent two important cardiovascular risk factors. Mortality and morbidity associated with CVD are elevated in overweight individuals, particularly in the presence of visceral deposition of adipose tissue [76]. More recently, it has become evident that obesity is invariably accompanied by a significant decrease in plasma adiponectin levels and that adiponectin has many defensive properties against obesity-related diseases, such as hypertension.

Accumulating evidence suggests that dysfunctional innate and adaptive immune and inflammatory responses, along with the overproduction of oxidants, contribute to the pathogenesis of vascular dysfunction and hypertension in obese patients. The effect of obesity on vascular function may be mediated by the hormone leptin has been shown to have angiogenic activity, increase oxidative stress in endothelial cells, and to promote vascular cell calcification and smooth muscle cell proliferation and migration. So, it is a major risk factor for the development of the atherosclerotic cardiovascular disease.

Obesity and Gastrointestinal Dysfunctions: Obesity is linked to gastrointestinal disorders, that can occur as gastro-oesophageal reflux disease, dyspepsia, constipation, irritable bowel syndrome, diarrhea, bloating, and other nonspecific conditions [77].

Preclinical studies, aimed at characterizing the molecular mechanisms underlying gastrointestinal disturbances in obesity, reported that diet-induced obesity determines a remarkable morpho-functional remodeling of the enteric neuromuscular compartment, followed by alterations in gut transit [78]. Evidence indicate the presence of increased mucosal permeability and changes in the intestinal microbiota, along with low-grade enteric inflammation and oxidative stress in the bowel tissues of obese animals, leading to hypothesize a critical role of this phlogistic condition in the pathophysiology of intestinal dysfunctions associated with obesity.

Although, several studies have implicated the adipose tissue as being primarily responsible for obesity-associated inflammation, the most recent findings have correlated the impairments of intestinal immune homeostasis and mucosal barrier with increased activation of inflammatory pathways and the development of insulin resistance. On this basis, it is now essential to characterize the mechanisms underlying obesity-associated gut alterations for developing novel therapeutic approaches to prevent obesity and its associated diseases.

Investigator demonstrated the potential health benefits of natural flavonoids in treating obesity and DM, mechanism of action on multiple molecular targets and would provide insight into the field of drug discovery and development. The anti-obesity and antidiabetic potential of flavonoids are very large given their regulatory effects on blood sugar transporters by increasing insulin secretion, reducing apoptosis, promoting pancreatic beta-cell proliferation, and reducing insulin resistance, inflammation, and oxidative stress in the muscle [79].

Accordingly, *in-vitro* and *in-vivo* studies have suggested the anti-obesity activity of several flavonoids isolated from fruit and plant extracts.

A summary of major findings obtained with flavonoids in counteracting obesity and related disorders in experimental models and in epidemiological/clinical studies (see **Table 4** and **Table 5**) [60, 80].

TABLE 4: MAJOR FLAVONOIDS SUBCLASS AND DIETARY FOOD SOURCE

Flavonoid Subclass	Dietary Flavonoids	Common Food Sources
Anthocyanidins	Cyanidin	Red, blue, and purple berries: Red and purple grapes, red wine
Flavanols	Monomers (Catechins): Catechin, Epicatechin, Epigallocatechin gallate. Dimers and Polymers: Proanthocyanidins	Catechins: Teas (particularly green and white), chocolate, grapes, berries, apples. Theaflavins and Thearubigins: Teas (particularly black and oolong). Proanthocyanidins: Chocolate, apples, berries, red grapes, red wine
Flavanones	Naringin/Naringenin, Eriodictyol	Citrus fruit and juices, *e.g.*, Oranges, grapefruit, lemons
Flavonols	Quercetin, Myricetin	Yellow onions, scallions, kale, broccoli, apples, berries, teas
Isoflavones	Genistein	Soybeans, soy foods, legumes

TABLE 5: SUMMARY OF THE EFFECTS OF FLAVONOIDS IN COUNTERACTING OBESITY AND RELATED DISORDERS IN EXPERIMENTAL MODELS

Flavonoid	Experimental model	Outcome
Anthocyanins [81]	HFD-fed mice	The decrease in systemic inflammation; prevention of chronic hypertension progression
Catechin [82]	HFD-fed mice	Improvement of brain and pancreas functions
Naringin [83]	HC and HFD-fed rats	The normalisation of systolic blood pressure, improvement of vascular and cardiac dysfunction, decrease in plasma lipid concentrations, oxidative stress and inflammatory cell infiltration, improvement of liver mitochondrial function
Quercetin [84]	HFD-fed mice	Decrease in body weight gain; decrease in adipose tissue macrophage, infiltration and inflammation, through the modulation of AMPK and SIRT1, improvement of insulin sensitivity and glucose intolerance
Genistein [85]	Obese diabetic mice	The decrease in hyperglycemia-induced monocyte adhesion; improvement of vascular inflammation

CONCLUSION: The WHO report stated that obesity had reached epidemic proportions worldwide. Since then its incidence has continued to rise at an alarming rate in both developed and developing countries and is becoming a major public health concern with incalculable social costs. Although, the therapeutic management of obese patients includes modifications in their lifestyles, adequate diet and exercise workshop and proper control of weight are often low and disappointing.

Unsatisfactory outcomes after cessation of the lifestyle modification or pharmacotherapy, compelled the researchers and physicians to rethink to find a new, safe, and outstanding therapeutic alternative that has better efficacy and lower adverse effect for this global health issue. Recent researches show different medications having anti-obesity effects by several mechanisms including exenatide a glucagon-like peptide acting as an incretin hormone, lorcaserin a novel selective serotonin-2C receptor agonist that modulates food intake in hypothalamus and PYY 3-36 and oxyntomodulin, a glucagon-like peptide 1 receptor agonist that regulate food intake. Natural drugs have been introduced to draw attention as an effective alternative to reduce body weight and alter other metabolic risk factors.

While the etiology of obesity is multi-faceted, oxidative stress and related inflammatory conditions represent potential and useful targets. Determining the molecular mechanisms involved in glucose and lipid metabolism in obesity and diabetes would provide insight into the field of drug development, and future discoveries are expected to yield therapeutic benefits. The strongest conclusion that can be drawn from the revision of current literature is that some flavonoids offer novel therapeutic approaches to prevent obesity and related co-morbidities through their capacity of reducing adipose tissue mass, thereby decreasing intracellular free radical formation, increasing antioxidant defenses and attenuating inflammatory signaling pathways, mostly from studies in animal models. Till date, although continuous efforts are being made in this research area, additional studies are still required to elucidate the value of dietary flavonoids in the

context of public health or clinical practice in a better way. The phytoconstituents present in herbal plants have been identified, and target and definite mechanism of action can be determined. Hence, revealing those dietary constituents is promising for further research. Emerging studies have described the potential role of flavonoids in treating obesity and diabetes, as well as their associated metabolic diseases. Regulatory effects of flavonoids on blood sugar transporters by increasing insulin secretion, reducing apoptosis, promoting pancreatic β-cell proliferation, and reducing insulin resistance, inflammation, and oxidative stress in the muscle are associated with their anti-obesity and anti-diabetic potential.

Also, a better elucidation of the molecular mechanisms underlying the beneficial effects of flavonoids, using *in-vitro* and *in-vivo* experiments, would provide insights into the field of drug development for the management of obesity. Further, studies are needed to clarify the mechanisms underlying the action of flavonoids.

These studies provide a strong rationale for well-powered, randomized placebo-controlled intervention trials to be performed in patients with diabetic complications. Randomized controlled studies should also be performed in combination with current anti-obesity drugs, as the action of flavonoids may be most effective as an adjunctive rather than a primary therapy.

The results of this kind of reviews can be helpful for pharmaceutical industries to study on the components of these flavonoids and investigate further to find a mixture of those components with higher efficacy. In conclusion, future multi-disciplinary approaches, involving epidemiological and clinical investigations, are required to characterize further the potential beneficial effects of both plant-isolated flavonoids and flavonoid-rich foods in counteracting obesity and related disorders.

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