International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 4, 2024

Review Article

ANTI-OBESITY NUTRACEUTICALS: INSIGHTS INTO MECHANISMS OF ACTION AND POTENTIAL USE OF BIOCOMPATIBLE NANOCARRIERS FOR DELIVERY

DOAA SALAH ELDIN ABDELFATTAH[1,2*], MERVAT A. FOUAD[1], ALIAA N. ELMESHAD[2,3], MOHAMED A. El-NABARAWI[2], SAMMAR FATHY ELHABAL[4]

[1]National Nutrition Institute, Cairo-11435, Egypt. [2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Giza-11562, Egypt. [3]Department of Pharmaceutics, Faculty of Pharmacy and Drug Technology, The Egyptian Chinese University, Cairo-11786, Egypt. [4]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Modern University for Technology and Information (MTI), Cairo-11571, Egypt

[*]Corresponding author: Doaa Salah Eldin Abdelfattah; [*]Email: dofattah@gmail.com

Received: 01 Mar 2024, Revised and Accepted: 01 May 2024

ABSTRACT

One of the serious health issues that has detrimental effects on health is obesity. Obesity is associated with common comorbidities like diabetes, dyslipidemia, and cardiovascular diseases. New understanding of the pathophysiologic mechanisms underlying obesity has led to the development of several novel agents and effective strategies to combat the global obesity epidemic and its comorbidities. The objective of managing obesity has changed to include both reducing its complications and helping people lose weight. Although there are more pharmaceutical options available for managing obesity, their efficacy and safety profiles are either limited or moderate. While behavior interventions and active lifestyle remain the cornerstones of successful weight loss, it can be very challenging to maintain such a healthy lifestyle. Thus, new agents that are safer and more effective are therefore urgently needed. Natural products and dietary supplements have been demonstrated as a potential treatment for obesity. Recent studies suggested that propolis, chromium picolinate, and White Kidney Bean Extract (WKBE) may have anti-obesity properties. This review provides an overview on the anti-obesity effects of these natural products, their active ingredients and mechanisms of action. In addition to potential cutting-edge delivery techniques that can be applied to maximize the anti-obesity effects of these bioactive substances with varying solubility, bioavailability, and stability.

Keywords: Obesity, Nutraceutical, WKBE, PEE, $CrPic_3$, Biocompatible carriers, Drug delivery system

DOI: https://dx.doi.org/10.22159/ijap.2024v16i4.50773 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Lately, obesity has evolved into a significant worldwide public health concern. In addition to making our bodies out of shape, obesity negatively impacts our health [1]. Clinical research has demonstrated a connection between obesity and the onset and development of a number of chronic metabolic disorders, including insulin resistance, dyslipidemia, and persistent inflammation [1]. In accordance with how serious the illness is and coexisting disorders, obesity can even shorten life expectancy by 5 to 20 years for a number of chronic metabolic diseases, such as cardiovascular disease, type 2 diabetes, and cancer [2]. There is increasing evidence that the most effective approach to treating and preventing obesity is through dietary intervention. Recently, the use of natural plant extracts as an alternate strategy for treating obesity has gained interest. It has been discovered that a variety of naturally occurring substances, including polyphenols, glycoproteins, peptides derived from plants, and polysaccharides, can prevent obesity by preventing the differentiation of adipocytes [2]. One of the common food used in both Africa and South America is the white kidney bean (*Phaseolus vulgaris l.*), which is gaining popularity across the globe for its established ability to prevent obesity [3, 4]. The extract from white kidney beans is especially intriguing since it includes a protein-based alpha-amylase inhibitor (α-AI) that acts as a "starch blocker", where the target enzyme is α-amylase, a crucial enzyme that aids in the breakdown of carbohydrates. α-AI has the ability to suppress the amylase enzyme, obstruct the food's starch hydrolysis, and lessen the breakdown of complex carbohydrates. Because of these findings, white kidney bean extract is a potentially effective option for glycemia, body weight, lipid build-up, and food consumption disorders [5]. Another natural product that has drawn interest is propolis, which showed a variety of biological benefits. Propolis is a naturally occurring product that bees provide, and it has been used as a folk remedy since ancient times. Several pharmacological outcomes have been demonstrated, including antioxidant, immunomodulatory, antitumoral, antimicrobial, antiviral, antifungal and anti-inflammatory properties [6]. Even though research revealed that the composition of propolis differs according to its source, location, season, hives, and part of the plant used by the bees, polyphenols continued to be the most important factor in controlling insulin resistance, lipid metabolism, and weight loss which contributed to the propolis's potent anti-obesity effects shown in both *in vivo* and *in vitro* research [7]. Lastly, a trace element that is extensively present in the diet of humans is chromium (III) picolinate ($CrPic_3$), an organic trivalent chromium compound complexed with a naturally occurring tryptophan derivative complexed with picolinic acid. Despite the fact that the precise mechanism of chromium remains unclear, it is commonly marketed as a weight loss aid. The majority of research indicated that this effect is related to the metabolism of fats and carbohydrates, where it might play a significant role in enhancing the ability of insulin to regulate blood sugar [8]. Consequently, $CrPic_3$ may be able to control eating patterns food cravings, reduce hunger, promote thermogenesis, increase resting metabolic expenditure, and increase insulin sensitivity [9].

Combining bioactive substances or extracts can lead to synergistic or additive effects through a variety of mechanisms, including multi-target effects, increased bioavailability, increased bioactivity, or neutralization of the mixture's harmful effects [10-12]. However, one of the challenges of combining different bioactive compounds is that they can have different solubility, chemical stability and bioavailability. A current overview of the wide variety of uses for nanocarriers can be found in biocompatible nanocarriers. Nutraceutical delivery systems based on biocompatible nanocarriers can enhance oral bioavailability by lowering first-pass metabolism in the gut and liver, increasing nutraceutical solubility in intestinal fluids, and stabilizing nutrients in the gastrointestinal tract. Biocompatible nanocarriers delivery methods are various, including those involving proteins, lipids (nano-emulsion, liposome-mediated delivery systems) and carbohydrates [13]. The purpose of this review is to present the current data on the anti-obesity effect of these natural products while providing an overview on novel delivery systems that may be able to help offer a combination of these anti-obesity bioactive compounds in a single dosage form with the aim of maximizing their overall anti-obesity effects. This review

article used keywords such as WKBE, propolis, chromium picolinate, anti-obesity mode of action, nutraceuticals, drug delivery systems, nanoparticles, and biocompatible nanocarriers. It is written based on the literature that is available from 2010 to 2024 gathered by various sources such as PubMed, Google Scholar, Research Gate, and Science Direct.

Obesity

Owing to changes in lifestyle and societal advancements, obesity is now a significant public health issue. After smoking, obesity is the second biggest risk factor, directly leading to 3.4 million deaths per year [14]. According to a World Health Organization (WHO) report from (2021), the number of adults who are obese has nearly tripled from 1975 to 2016. Of these adults, over 650 million were obese and over 1.9 billion were overweight. Childhood and adolescent obesity is a severe issue; in 2016, over 340 million children and teenagers between the ages of five and nineteen were obese or overweight, a 14% increase since 1975 [14]. Despite the fact that obesity was previously considered a problem in high-income nations only, it is now widespread in low and middle-income nations. According to PROCON organization (2020), Egypt is ranked as the 18th country with the highest prevalence of obesity in the world. It is reported that rates of obesity in Egypt has reached 39.8% among adult Egyptians aged ≥ 18 y [15]. According to reports, the percentage of adult Egyptians aged 18 and older who are obese has reached 39.8% [15].

Obesity is the leading cause of preventable death globally, acting as a proxy for multiple comorbidities due to its increased morbidity and mortality rates. Obesity-related illnesses include a higher risk of heart disease, hypertension, osteoarthritis in the knee, dyslipidemia, sleep apnea, type 2 diabetes, and certain malignancies [16, 17]. Obesity has recently been discovered to be a significant risk factor for hospitalization and a poor clinical outcome for SARS-CoV2 patients during the COVID-19 pandemic [18]. Obesity not only lowers an individual's quality of life significantly, but also epidemiological studies have linked obesity to the onset and progression of several chronic metabolic diseases, including insulin resistance, abnormal glucose metabolism, abnormal lipid metabolism, and chronic inflammation [19].

Pathogenesis of obesity and treatment strategies

Even though it's unclear what specifically causes obesity, it is generally accepted that environmental (acquired) and genetic (congenital) factors work together to determine the disease's pathophysiology [19, 20]. The risk of obesity is increased by a number of factors, including a rise in sedentary behavior and poor eating habits, such as eating eating food that is low in fiber, high in saturated fats, and high refined sugars. A continuous discrepancy between energy consumption and intake leads to obesity, where excess of energy is not used up and is instead turned into fat and stored in adipose tissue. This leads to an abnormal build-up of adipose tissue and an increase in its weight, particularly in the adipose tissue around the abdomen [20]. Insulin resistance results from cells being in a state of high encircle energy during fat accumulation when energy intake is lower than energy expenditure for an extended period of time. This lowers the effectiveness of insulin in facilitating the uptake and utilization of glucose, which leads to compensatory excessive secretion of insulin, causing insulin resistance. It is noted that insulin resistance causes cells to use less energy, which in turn alters the body's energy intake and consumption balance, ultimately resulting in obesity [21]. Changes in serum lipid levels are the primary indicator of abnormal lipid metabolism. Changes in serum lipid levels, which include an increase in triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL) and a decrease in high-density lipoprotein (HDL), are primarily caused by either excessive lipid intake or the conversion and accumulation of fat in the body [1, 22]. Treatments for obesity encompass a wide range of approaches to reduce weight and lessen obesity-related complications, such as dietary adjustments, calorie restriction coupled with increased physical activity, lifestyle modification, prescription weight-loss drugs, and weight-loss surgery [23]. The National Heart, lung, and Blood Institute's "Pharmacological Management of Obesity: An Endocrine Society Clinical Practice (ESCP) Guideline" states that balanced diet and lifestyle modifications combined with moderate-intensity exercise are the best ways to treat obesity [24]. Providing fast weight loss techniques, obese patients may feel more empowered to make lifestyle changes and be more assured of their ability to achieve their goals. It may seem that weight-loss medications are the answer to obesity. However, potential negative drug reactions or side effects are a constant source of concern for the public's health and an important challenge to the development of novel pharmaceutical products. For instance, due to potential harm to heart valves, two medications used for weight loss, fenfluramine and dexfenfluramine (Redux), were taken off the market in 1997. The year 2010 saw the withdrawal of sibutramine, also known as Meridia, due to an elevated risk of heart attack and stroke. In response to reports of severe liver damage brought on by the weight-loss medication "Xenica" the FDA approved a revised drug label that year that included safety information about possible side effects [23]. Although anti-obesity drugs might appear to be a good option, their lack of effectiveness, potential negative effects, and drug interactions emphasize the need for new, effective, and safe anti-obesity ingredients. The undesirable side effects of synthetic medications have led to the preference for natural products due to their efficiency in treating obesity and numerous other chronic conditions. Creating functional products from everyday foods is arguably the most well-liked market niche for the functional supplement industry. The worldwide market for dietary supplements and nutraceuticals is vastly growing. When it comes to application-specific market segmentation, the dietary supplement market's overall revenue is significantly influenced by the weight loss segment. Over the projection period of 2015–2025, weight loss market is anticipated to expand at a 7.4% compound annual growth rate [24].

Natural products still make up a substantial amount of pharmaceutical agents and have historically been instrumental in helping to alleviate a number of health issues. For instance, more than 60% of the anticancer medications on the market today, including vinblastine, camptothecin, and taxol, have natural sources [25]. Moreover, natural products aid in the discovery of bioactive substances that serve as the foundation for the creation of anti-inflammatory medications. The best illustration is provided by polyphenolics, which act as biomarkers and modulate inflammatory pathways to prepare therapeutic agents for the management of inflammatory disorders. Furthermore, some antidiabetic medications, like the popular medication metformin, were created using natural resources [26].

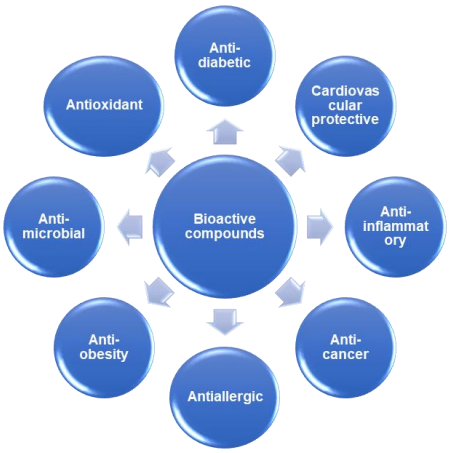

Fig. 1: Different uses of bioactive compounds

Functional ingredients and anti-obesity mechanisms of few natural health products in the market

A lot of research has been done on natural supplement products that mainly aid in the fight against obesity. The majority of the active ingredients in natural products come from plants, which include fruits, vegetables, grains, and herbs. These foods also contain a significant amount of dietary fiber, functional fatty acids (such as conjugated and polyunsaturated fatty acids), and phytochemicals [25, 26]. Below are three promising natural products with bioactive compounds claimed to have anti-obesity properties.

White kidney bean (*Phaseolus vulgaris l.*)

According to a recent meta-analysis, obese people can effectively improve their weight control by including a higher proportion of legumes in their daily diet. White kidney beans (*Phaseolus vulgaris*) belong to the family Fabaceae and genus *Phaseolus*. It is rich in protein, dietary fiber, unsaturated fatty acids, starch and vitamins. It makes up half of the indirect human consumption of grain legumes and is widely consumed worldwide. It is acknowledged in many Asian, latin American, and African nations as the primary source of dietary protein. China's adult population between the ages of 18 and 59 consumed 62.1% beans in 2015; where the average daily consumption for the entire population was 1.1g [27].

Due to its well-documented ability to reduce obesity, white kidney beans have attracted attention from all over the world. Alpha-amylase inhibitor (α-AI), a natural glycoprotein built up in the seeds to keep pets away, accounts for roughly 9–11% of the total protein content in the seed. Approximately seventeen days after pollination, the a-AI can be detected in the plant seed's cotyledons and axis. While after 28 d, the amounts rise to a fixed maximum until maturity. Despite potential yield limitations due to the extraction process, this percentage can yield a significant amount of the inhibitor from a given quantity of common beans [28]. The α-AI in the WKBE has been shown to suppress the function of α-amylases, an essential enzyme for the metabolism of starch, making it a target for the treatment of issues related to weight and obesity, including dyslipidemia and postprandial hyperglycemia [28]. Briefly, α-amylase is a glycoprotein tetramer (α-1,4-glucan-4-glucanohydrolases) with a molecular weight that varies between 15 and 56 kDa. It is responsible for catalyzing the endo-hydrolysis of (1→4)-α-D-glycosidic linkages in polysaccharides containing three or more (1→4)-α-linked D-glucose units. α-amylase is one of the main enzymes found in the pancreas and salivary glands, essential for both the absorption of simple sugars and the digestion of starch. When α-D-(1-4) glycosidic bonds are broken, shorter oligosaccharides known as dextrins are released. These are then further hydrolyzed and the resultant sugars are absorbed. As such, α-amylase is an essential step in the breakdown and absorption of dietary polysaccharides and inhibiting it can lower the glycemic peak, the rate at which carbohydrates are absorbed, and the amount of real energy consumed after a meal [28].

The anti-obesity, anorexigenic, and reduction of postprandial plasma hyperglycemia and insulin effects of WKBE have been demonstrated by numerous *in vivo* investigations conducted on animal and human models. Data indicated that rats' body weight decreased and their food intake decreased after using varying doses of WKBE (0, 50, 200, and 500 mg/kg) for 10 days [29]. Similar information from an additional investigation demonstrated a reduction in lipid accumulation and body weight gain in rats given a diet rich in α-amylase inhibitors [30]. Compared to control rats given a vehicle, the impact of daily intragastric gavage administration of a single dose (50 mg/kg) of WKBE for 21 consecutive days on daily food intake and body weight in Wistar rats resulted in a 15% reduction with a reduction in body weight gain by (-1.3 g/rat) in the experimental group versus a gain (+52.0 g/rat) in the control [31]. Two additional studies compared the effects of prolonged (700–800 days) exposure to a diet high in starch that contains 90 g/kg of WKBE to a control group that received a diet free of WKBE. They discovered that the test group of rats had significantly lower feed efficiency than the control group, particularly during the first three months of the study, where body weight increase over food intake is the definition of feed efficiency [27]. At the same time, one of the two studies found that the test group's body fat content was substantially lower than that of the control group. In contrast, the test group in the other study had a mean body weight gain of about 470 g, and the control rats had a mean body weight gain of about 660 g. Another study that fed Wistar rats a daily single dose of WKBE (100 mg/kg) for 22 straight days verified the above results. It showed that the rats' body weight increased less than 25% while their daily food intake decreased [31].

In 2000, the first trial study that was double-blind, randomized, and placebo-controlled was conducted to see if white bean extract could help with weight loss. A tablet comprising 200 mg of inulin, 50 mg of *Garcinia cambogia* extract, and 200 mg of WKBE was used in the study. For a duration of three months, the dosage of two tablets was administered after each of the three meals forty volunteers who are overweight but otherwise in good health, having a BMI ranging from 27.5 to 39. The tested group experienced a significant decrease in body fat percentage, BMI, and weight loss. Not only did these results validate the initial findings in the animal models, they also demonstrated that gastric juices have no effect on the inhibitory activity. Furthermore, it was concluded that α-AI from WKBE lowers GIP levels, blood glucose, C-peptide, the absorption of complex carbohydrates with essentially negligible negative side effects [37].

Based on literature review, α-AI prevents starch breakdown by blocking access to the enzyme's active site, which is why it has an effect on food intake, body weight, and glycemia. By competitively inhibiting starch's binding with carbohydrates, α-AI prevents starch from reaching the active site of the amylase enzyme. α-AI blocks the substrate-reducing end of the enzyme and utilizes a steric hindrance mechanism to block the non-substrate-reducing end, affecting all of the enzyme's catalytically capable regions, thus delaying the carbohydrate digestion in the gastrointestinal tract. Research has also demonstrated that α-AI efficiently lowers intraluminal amylase activity throughout the entire gastrointestinal tract, which lowers the rate at which glucose evolves and absorbed in the lumen [38]. This lowers the amount of carbohydrates that are absorbed and digested, which reduces the amount of calories that come from carbohydrates. In turn, this potentially aid in weight management by lowering the total caloric load derived from diet carbs. resulting in the body's stored fat being mobilized as a result of energy restriction [36, 37, 39].

Another underlying mechanism for the α-AI's anti-obesity action was believed to be its anorexigenic effect. While the precise mechanism underlying the α-AI's anorexigenic effect remains unclear, certain research findings indicate that rats given the amylase inhibitor on a long-term basis showed a decreased food intake [39]. Subsequent research revealed that the anorexigenic effect of the inhibitor might only be attained through extended exposure, as the Sprague-Dawley rats only exhibited anorexia after 77 days of administering α-AI. Additionally, it has been documented that α-amylase inhibitors postpone the emptying of the stomach, causing a sense of fullness that leads to a decrease in food consumption [36].

Meals containing the amylase inhibitor were found to reduce insulin levels and postprandial plasma hyperglycemia in rats. In human studies, taking an amylase inhibitor before or with a meal high in starch resulted in a 85% reduction in the postprandial plasma glucose integrated area and a lower late postprandial plasma glucose level compared to fasting. This was explained to be due to reducing the digestion and absorption of carbohydrates, it can prevent rapid spikes in blood sugar levels after meals [37, 38].

A number of research studies have substantiated the safety and advantageous application of α-AI derived from white kidney beans in managing obesity. No significant adverse effects, such as those affecting liver and renal function or blood counts (including white blood cells, hemoglobin, and platelets) have been reported for either short-term or long-term use. However, consumption of WKBE not only lead to the inhibition of digestion and absorption of carbohydrates but also has demonstrated notable modifications to the diversity and composition indices in the form of increase in methane, carbon dioxide and hydrogen. Consequently, these changes alter the delivery of substrate to the gastrointestinal tract, in particular the bacteria that live there and are associated with bloating, flatulence, and diarrhea. Overall, WHO claims that WKBE can be used safely as a diet supplement. Provided information indicated that WKBE is safe to eat and well tolerated, even with greater dosages of 3000 mg per day and extended periods of supplementation [40].

Propolis

The term "propolis" was originated from the Greek "pro," meaning "the entrance of" and "polis," which means "city of bees." This term is appropriate for suggesting that the product has the ability to protect the honeycomb's entrance. Propolis functions as a kind of chemical defense against pathogenic germs such as viruses, bacteria, and other microbes that can proliferate throughout the hive. Bees gather propolis, a natural resinous complex substance, from the buds and exudates of specific plant sources. They combine propolis with beeswax, and when bee salivary enzymes (β-glucosidase) are present, the substance turns into a viscous, dark-colored product [41]. Propolis has been utilized by numerous civilizations throughout history. Propolis was the main component used to preserve corpses in ancient Egypt and in Galneo and Dioscorides, where both employed it as an antibacterial and wound-healing substance. The Greeks, including Aristotle and Hippocrates, recognized it as a form of both internal and external medicine [41]. Propolis is mentioned by Pliny the Roman historian as a remedy for pain and edema. Propolis has been approved by the london Pharmacopoeia as a medication. In the succeeding centuries, the medical benefits of propolis have drawn significant interest, especially in Eastern Europe. Propolis was widely utilized in South Africa at the close of the nineteenth century because to its therapeutic qualities, and during World War II, it was employed by a number of Soviet physicians. The first scientific paper on the chemical makeup and characteristics of propolis was published in 1908, and the first patent was issued in 1965. In traditional medicine, propolis has become more well-known for its many biological properties, which include antiviral, anti-inflammatory, antioxidant, antibacterial, and immunoregulatory effects. Currently, the market offers a wide variety of propolis products as a food and beverage additive, as well as to promote health and protect the body from diseases like diabetes, cardiovascular disease, and cancer [42-45]. Propolis can be found as extracts (liquid or powder) in bottles, capsules, pills, vaporizers, syrups, and lotions, among other forms. Propolis is also frequently utilized in goods intended to promote immunity as well as those for wound healing and oral health [46]. Numerous studies have been inspired by the widespread interest in propolis to look deeper into its bioactivity and positive health effects.

The composition of propolis varies according to its botanical source, location, season, hives, and the parts of the plant that bees can access. It can be found in a variety of colors, including red, green, and brown, as well as in various physical stages depending on the climate. In general, propolis is composed of 50–55% resin (primarily flavonoids, phenolic acids, and esters), 10% volatile substances, 30–40% beeswax, 5–10% pollen, and other materials. The anti-obesity impact, however, was concentrated on three types of propolis: Dalbergia type, Baccharis type, and Poplar type [47]. Belonging to the Poplar-type botanical source family, Egyptian propolis is widely distributed throughout North Africa, most of Asia, Europe, and North America. The composition of propolis varies, but over 300 chemicals have been identified as flavonoids, including flavones and flavonols, and free phenolic acids and their esters [48]. Over the past few decades, many research have examined and reported the weight reduction effects of propolis polyphenols in both humans and animals. These investigations revealed that in high-fat diet-fed mice propolis extract could increase lipid metabolism, decrease insulin resistance and manage obesity. The caffeic acid phenethyl ester (CAPE) and p-Coumaric acid phenolic chemicals found in propolis have been linked to a number of biological and pharmacological effects. Brown adipose tissue's thermogenesis has been observed to be enhanced by P-coumaric acid [49-55]. On the other hand, caffeine offers a host of advantageous biological characteristics, such as the ability to inhibit adipogenesis, reduce insulin resistance, suppress the expression of intestinal microbes and hepatic lipogenic genes. These effects can help prevent hyperlipidemia and obesity in rats [56]. A different study discovered that out of the three different propolis botanical sources, poplar-type had the most significant anti-obesity effect in high-fat-fed mice. According to this study, the distinct polyphenol molecule called caffeic acid that is present in poplar propolis extract may be responsible for this outcome [57]. Studies have demonstrated, as fig. 2 illustrates, that propolis-derived compounds influence mice's lipid metabolism-related proteins, including 3-Hydroxy-3-Methylglutaryl-Coenzyme-A (HMG-CoA), sterol regulatory element binding protein-1 (SREBP-1), and peroxisome proliferator-activated receptor alpha (PPAR-α). These effects, in turn, influence lipid metabolism and the expression of fat accumulation, improving dyslipidemia and body fat accumulation [58]. Furthermore, propolis ethanolic extract can control blood lipid concentration, blood glucose, and glucose metabolism in rats with induced diabetes mellitus and insulin resistance, as previously described, where propolis significantly improve insulin resistance and blood glucose and lipid [59-62]. Other research has indicated a possible connection between modifications in the gut flora and the anti-obesity properties of propolis' polyphenols. Type 2 diabetes, insulin resistance, obesity, and other metabolic disorders that are strongly associated with long-term, low-grade inflammation may be significantly influenced by gut bacteria [63]. In mice fed a high-fat diet, the effects of propolis on the makeup of the gut microbiota and its anti-inflammatory properties were studied. It was discovered that 0.2% crude propolis corrected the gut microbial disruptions caused by the high-fat diet and decreased the levels of circulating lipopolysaccharides and inflammatory responses [64]. Similarly, a different study found that 1% or 2% ethanol extract of propolis supplementation decreased the buildup of hepatic fat and weight gain caused by high-fat diets. The study attributed these results to propolis's ability to modify the structure and functioning of the gut microbiota [65].

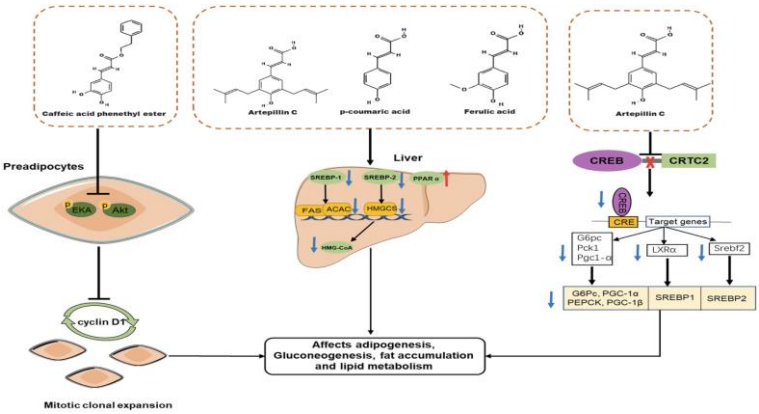

Fig. 2: Impacts of substances derived from propolis on fat storage, adipogenesis, and lipid metabolism [58]

Chromium (III) picolinate ($CrPic_3$)

A crucial cofactor for insulin function, chromium (Cr^{3+}) is an important nutrient (trace element) needed for the proper metabolism of proteins, fats, and carbohydrates. The human diet contains a wide variety of foods that are high in chromium, such as meat, nuts, cereal grains, molasses, and brewer's yeast. Supplemental chromium has enhanced glucose metabolism and insulin sensitivity, lowering blood glucose levels in overweight diabetics [66]. The range of 25–45 µg/d is recommended by current dietary guidelines for adults, while the amount of chromium absorbed from the food is thought to be between 1% and 2% [67]. To improve absorption in the gastrointestinal tract, trivalent chromium is complexed with picolinic acid, a naturally occurring tryptophan derivative, to form chromium (III) picolinate ($CrPic_3$). It is an over-the-counter nutritional supplement that has been recommended by doctors to treat type 2 diabetes, help people lose weight, and build muscle [68, 69]. Previous studies have shown that administering a dose of 200–1000 ug/d for 12 weeks on average changed the BMI of the chromium groups and significantly reduced their body fat percentage and body weight in comparison to the control group [70-73].

Despite the specific method of action of $CrPic_3$ is unclear, it is thought to be linked to its ability to lower body fat percentages and effects that increase insulin sensitivity by either extending increasing insulin receptor sensitivity or insulin activity which could lead to improved glucose metabolism and improved blood sugar regulation. According to some other theories, chromium may have an impact on neurotransmitters that regulate eating patterns, reduce appetite, and curb food cravings, all of which may result in a reduction in caloric intake. In addition, Cr^{3+}has the potential to boost thermogenesis via enhancing insulin action and boosting insulin-sensitive glucoreceptors in the brain. It is thought that Cr^{3+} interacts with the insulin receptor by either oxidizing Protein-Tyrosine Phosphatase 1B's (PTP1B) which is an essential cysteine residue in the active site, and has also been reported to cause irreversible inhibition of PTP1B, or by stimulating the tyrosine kinase pathway, improving glucose absorption [72, 73].

Innovative/novel nutraceutical delivery systems

"Nutraceutical," a term that originates from the words "nutrition" and "pharmaceutics," refers to products that have been separated from herbal products, nutritional supplements, and particular diets that are used for health-related reasons other than nutrition [74]. Nutraceuticals have demonstrated numerous positive effects in the treatment and prevention of numerous health issues, including but not limited to cancer, inflammation, hypertension, cardiovascular diseases, atherosclerosis, obesity, and diabetes [75]. Unfortunately, some bioactive compounds have a number of weaknesses and restrictions, including poor solubility, low permeability, rapid metabolism, and chemical and physical deterioration [76]. Hence, was the need to introduce novel drug delivery systems that aims to improve the bioavailability, pharmacokinetics, efficacy and safety of nutraceutical products [77]. The incorporation of nano delivery systems in nutraceuticals is getting the most attention as a promising method for protecting and delivering bioactive components with better efficiency, efficacy, biocompatibility, and bioavailability due to improved absorption and stability against degradation [78-80]. Various nano-technology novel systems have been described including nano-encapsulation where the central material is enclosed with a solid or liquid wall material forming a nano capsule, nanosphere or Solid lipids Nanoparticles (SLNs) [80]. The benefits of polymer-based nano-delivery systems, which include the use of proteins, lipids, and polysaccharides, were examined in earlier research.

However, this improvement comes in with a huge disadvantage which is causing human toxicity [82]. There has been very little research done on the toxicity, distribution, metabolism, excretion, and absorption of nano systems. Consequently, further research is needed to understand how nanoparticles interact with biological systems in order to forecast the mode of action and ensure the security of the nano delivery system [83]. One theory states that the majority of the detrimental effects of nanoparticles are caused by the molecularly induced oxidative stress and inflammation [84]. Among the documented negative effects of nanoparticles are respiratory disorders, cardiovascular illnesses, carcinogenicity, and shortened life spans [85]. Putting into practice the guidelines recommended by the European Food Safety Authority (EFSA), a set of physicochemical parameters need to be assessed for nanoparticles in order to aid in the early assessment of nano systems toxicity and reduce the risk of drug withdrawal from the market due to safety issues from 50% to only 20% [86].

A current overview of the wide variety of biomedical uses for nanocarriers can be found in biocompatible nanocarriers such as those derived from organic and inorganic materials. Biocompatible nanocarriers are non-toxic, biodegradable, highly biocompatibility with blood, cells, and physiological conditions. Thus, they are currently the subject of more research in the biomedical sciences for the delivery of nutraceuticals and their use them in food processing, food packaging to achieve targeted bioactive ingredient delivery with the best possible therapeutic benefit, reduced toxicity and adverse effects. Generally, as shown in fig. 3, there are three types of biocompatible nanocarrier delivery systems: protein-based, lipid-based, and carbohydrate-based [87].

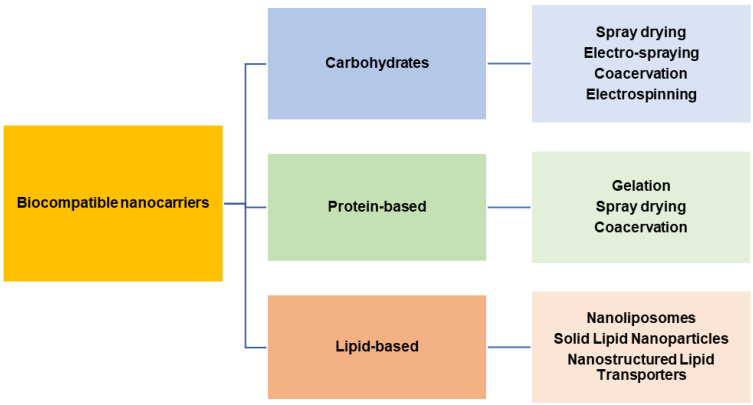

Fig. 3: Classification of biocompatible nanocarriers

Due to their special qualities of abundance and flexibility, carbohydrate delivery systems work well with a wide range of bioactive substances. These delivery methods are superior to lipid- and protein-based carriers because they remain highly stable even at elevated temperatures, while the latter are prone to denaturation and degradation. Currently, popular examples of carbohydrate-based delivery systems include cyclodextrin produced via nanofabrication techniques such as electro-spraying, coacervation, spray drying, and electrospinning. With a hydrophilic end on one side and a hydrophobic center cavity on the other, it is made up of a

condensed oligosaccharide. Enclosing bioactive ingredients that are less soluble, susceptible to temperature fluctuations, or chemically liable can be beneficial with these [88, 89].

Because plant-protein-based delivery systems have become more popular in the field of nanotechnology, nutraceutical fields have recently focused more on them in order to protect and manage lipophilic bioactive substances (carotenoids, vitamins, polyphenols, and polyunsaturated fatty acids) because of the multiple functional groups on their external surface [90]. Their primary sources are legumes, nuts, tuber, cereals, pseudo-cereals and oil/edible seeds, making them sustainable, eco-friendly and can easily be combined with other sources. Common techniques for creating protein-based delivery systems include electro-hydrodynamic processes, gelation, spray drying, and coacervation [91]. Plant-based proteins can be used to create an extensive variety of carrier structures, such as micro/nanoemulsions, nano-hydrogels and self-assembled films [92]. For example, nano-emulsions are either oil-in-water or water-in-oil colloidal dispersion system. They entrap bioactive compounds in their distribution phase that is stabilized by surfactants or biopolymers in the continuous phase [93]. Nanohydrogels are water-swellable nanoparticles created by combining hydrogel and nano-sized polymeric network that is water insoluble [94]. Nevertheless, this plant protein delivery system faces a challenge in that it only transports lipophilic bioactive compounds. Since, the properties of protein-based nanocarriers such as, spatial size, colloidal stability, water dispersibility is established by the physicochemical molecular principles of protein. Therefore, protein-bioactive molecule interactions have the ability to alter the characteristics of proteins and influence the carrier matrix's structural arrangement and dynamics. In order to verify their functional qualities, further investigations are required to validate their extraction and purification processes [95].

While carbohydrate/polysaccharide nanocarriers are used for their bioadhesive qualities, lipid-based delivery systems, such as nanoliposomes, SLNs and Nanostructured lipid Transporters (NLCs) are used for their biocompatibility, loading capacity, solubility, and bioavailability [76, 96-99]. Moreover, lipid-based delivery systems can trap ingredients with varying solubilities, enhance their delivery and protects their constituents against pH and enzymatic degradation, making the lipid-based nano delivery system the most advantageous encapsulation system with unmatched benefits over the other two systems. liposomes, for instance, are spherical vesicles with an aqueous cavity and a lipid bilayer membrane that combine to form a biocompatible, non-toxic dual carrier that can hold bioactive substances with distinct physicochemical properties in both the lipid bilayer and the core. liposomes enhance the solubility stability, along with the hydrophobic drugs' bioavailability. Nevertheless, liposomes have few disadvantages, including a short half-life, unstable nature, low loading capacity, and high cost [99].

To conclude, the alleged safety and effectiveness of nutraceuticals are driving their rapid growth in global consumption. More focus has recently been placed on the use of cutting-edge nanoscale drug delivery systems as a foundation for nutraceutical formulation. This is impacted by the encouraging outcomes found in relation to the tested nutraceuticals' bioavailability, safety, targeting, and stability. This review article reviews the best available research on the latest potential natural anti-obesity products as well as cutting-edge technologies in nutraceuticals formulation. It also emphasizes the necessity of implementing these novel delivery systems in order to combine various bioactive compounds in a single nutritional dosage form and maximize their benefits. However, using biocompatible biocarriers has limitations. The physiological environment's impact on their physicochemical properties makes their preclinical characterization challenging. Other limitations that is related to their safety and toxicity in humans include the size, shape, surface charge, method of administration and dose. Furthermore, the absence of both uniform and biorelevant standards for characterization and quality control made the transfer of nanocarriers from the bench to the bedside more difficult. Finally, as nanocarrier technology develops, it will eventually be necessary to develop scalable manufacturing techniques that make use of good manufacturing practices in order to produce nanomedicines with optimized bioavailability and excretion profiles [100].

CONCLUSION

Our review article discussed the pathophysiology, effects, and objectives of managing obesity, which include preventing obesity-related complications and losing weight. We discussed the characteristics and modes of action of WKBE, Propolis Ethanolic Extract (PEE), and $CrPic_3$, which have been shown in preclinical and clinical investigations to have anti-obesity properties and to offer a safe and efficient substitute for anti-obesity medications. In order to overcome the varying solubility, bioavailability, and stability of these bioactive substances and optimize their anti-obesity effects, our review suggested the use of novel nanotechnologies as delivery systems, with a focus on biocompatible nanocarriers. However, more reliable characterization methods, scalable optimization approaches, stability maintenance procedures, and safety guidelines are needed to achieve the full potential of the biocompatible biocarrier drug delivery system.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Doaa Salaheldin Abdelfattah and Sammar Fathy Alhabal-conceptualization; Doaa Salaheldin Abdelfattah, Mohamed A. El-Nabarawi and Sammar Fathy Alhabal-search methodology. Doaa Salaheldin Abdelfattah and Sammar Fathy Alhabal-writing, editing and reviewing. Mohamed A. El-Nabarawi, Mervat A. Fouad, Aliaa N. ElMeshad-reviewing and supervision.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6-10. doi: 10.1016/j.metabol.2018.09.005, PMID 30253139.
2. Bluher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15(5):288-98. doi: 10.1038/s41574-019-0176-8, PMID 30814686.
3. Neil ES, McGinley JN, Fitzgerald VK, lauck CA, Tabke JA, Streeter McDonald MR. White kidney bean (*Phaseolus vulgaris l.*) consumption reduces fat accumulation in a polygenic mouse model of obesity. Nutrients. 2019;11(11):2780. doi: 10.3390/nu11112780, PMID 31731665.
4. Thompson HJ, McGinley JN, Neil ES, Brick MA. Beneficial effects of common bean on adiposity and lipid metabolism. Nutrients. 2017;9(9):998. doi: 10.3390/nu9090998, PMID 28891931.
5. Shi Z, Zhu Y, Teng C, Yao Y, Ren G, Richel A. Anti-obesity effects of α-amylase inhibitor enriched-extract from white common beans (*Phaseolus vulgaris l.*) associated with the modulation of gut microbiota composition in high-fat diet-induced obese rats. Food Funct. 2020;11(2):1624-34. doi: 10.1039/c9fo01813a, PMID 32022058.
6. Pasupuleti VR, Sammugam L, Ramesh N, Gan SH. Honey, Propolis, and Royal Jelly: a comprehensive review of their biological actions and health benefits. Oxid Med Cell Longev. 2017;2017:1259510. doi: 10.1155/2017/1259510, PMID 28814983.
7. Anjum SI, Ullah A, Khan KA, Attaullah M, Khan H, Ali H. Composition and functional properties of propolis (bee glue): a review. Saudi J Biol Sci. 2019;26(7):1695-703. doi: 10.1016/j.sjbs.2018.08.013, PMID 31762646.
8. Albarracin CA, Fuqua BC, Evans JL, Goldfine ID. Chromium picolinate and biotin combination improves glucose metabolism in treated, uncontrolled overweight to obese patients with type 2 diabetes. Diabetes Metab Res Rev. 2008;24(1):41-51. doi: 10.1002/dmrr.755, PMID 17506119.
9. Docherty JP, Sack DA, Roffman M, Finch M, Komorowski JR. A double-blind, placebo-controlled, exploratory trial of chromium picolinate in atypical depression: effect on carbohydrate craving. J Psychiatr Pract. 2005;11(5):302-14. doi: 10.1097/00131746-200509000-00004, PMID 16184071.

10. Abdelfattah DS, Fouad MA, Elmeshad AN, El-Nabarawi MA, Elhabal SF. Anti-obesity effect of combining white kidney bean extract, propolis ethanolic extract and CrPi3 on sprague-dawley rats fed a high-fat diet. Nutrients. 2024;16(2):310. doi: 10.3390/nu16020310, PMID 38276548.
11. Ebrahimi B, Baroutian S, Li J, Zhang B, Ying T, Lu J. Combination of marine bioactive compounds and extracts for the prevention and treatment of chronic diseases. Front Nutr. 2022;9:1047026. doi: 10.3389/fnut.2022.1047026, PMID 36712534.
12. Panahi Y, Hosseini MS, Khalili N, Naimi E, Majeed M, Sahebkar A. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: a randomized controlled trial and an updated meta-analysis. Clin Nutr. 2015;34(6):1101-8. doi: 10.1016/j.clnu.2014.12.019, PMID 25618800.
13. Manocha S, Dhiman S, Grewal AS, Guarve K. Nanotechnology: an approach to overcome bioavailability challenges of nutraceuticals. J Drug Deliv Sci Technol. 2022;72:103418. doi: 10.1016/j.jddst.2022.103418.
14. World Health Organization. Obesity and Overweight. Available from: https://www.who.int/en/news-room/factsheets/detail/obesity-and-overweight [Last accessed on 14 May 2024]
15. Aboulghate M, Elaghoury A, Elebrashy I, Elkafrawy N, Elshishiney G, Abul Magd E. The burden of obesity in Egypt. Front Public Health. 2021;9:718978. doi: 10.3389/fpubh.2021.718978, PMID 34513789.
16. Saini J, lora SS, Gupta MC. Maternal obesity as a predictive marker for adverse pregnancy outcome: a case-control study. Asian J Pharm Clin Res. 2023;16:33-7.
17. Taroeno Hariadi KW, Hardianti MS, Sinorita H, Aryandono T. Obesity, leptin, and deregulation of microRNA in lipid metabolisms: their contribution to breast cancer prognosis. Diabetol Metab Syndr. 2021;13(1):10. doi: 10.1186/s13098-020-00621-4, PMID 33482868.
18. Mohammad S, Aziz R, Al Mahri S, Malik SS, Haji E, Khan AH. Obesity and COVID-19: what makes obese host so vulnerable? Immun Ageing. 2021;18(1):1. doi: 10.1186/s12979-020-00212-x, PMID 33390183.
19. Hu S, Wang L, Yang D, Li L, Togo J, Wu Y. Dietary fat, but not protein or carbohydrate, regulates energy intake and causes adiposity in mice. Cell Metab. 2018;28(3):415-31.e4. doi: 10.1016/j.cmet.2018.06.010, PMID 30017356.
20. Gariani K, Ryu D, Menzies KJ, Yi HS, Stein S, Zhang H. Inhibiting poly ADP-ribosylation increases fatty acid oxidation and protects against fatty liver disease. J Hepatol. 2017;66(1):132-41. doi: 10.1016/j.jhep.2016.08.024, PMID 27663419.
21. Kotsis V, Antza C, Doundoulakis G, Stabouli S. Obesity, hypertension, and dyslipidemia. Springer; 2019.
22. Kulmi M, Saxena G. Comparison of effects of sitagliptin and a combination of naltrexone and bupropion in high fat-diet induced obesity model in rats. Asian J Pharm Clin Res. 2022;15:119-23. doi: 10.22159/ajpcr.2022.v15i8.45002.
23. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U. Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342-62. doi: 10.1210/jc.2014-3415, PMID 25590212.
24. Jakab J, Miskic B, Miksic S, Juranic B, Cosic V, Schwarz D. Adipogenesis as a potential anti-obesity target: a review of pharmacological treatment and natural products. Diabetes Metab Syndr Obes. 2021;14:67-83. doi: 10.2147/DMSO.S281186, PMID 33447066.
25. Dietary supplements market-driven by increasing demand for health products: global industry analysis and opportunity assessment 2015-2025; Available from: https://www.futuremarketinsights.com/reports/dietary-supplements-market [Last accessed on 10 Aug 2023]
26. Cragg GM, Pezzuto JM. Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents. Med Princ Pract. 2016;25Suppl 2:41-59. doi: 10.1159/000443404, PMID 26679767.
27. Peddio S, Padiglia A, Cannea FB, Crnjar R, Zam W, Sharifi Rad J. Common bean (Phaseolus vulgaris L.) α-amylase inhibitors as safe nutraceutical strategy against diabetes and obesity: an update review. Phytother Res. 2022;36(7):2803-23. doi: 10.1002/ptr.7480, PMID 35485365.
28. Los FG, Zielinski AA, Wojeicchowski JP, Nogueira A, Demiate IM. Beans (*Phaseolus vulgaris l*.): whole seeds with complex chemical composition. Curr Opin Food Sci. 2018;19:63-71. doi: 10.1016/j.cofs.2018.01.010.
29. Pop AV, Ciulca S. Phenotypic variability of pod traits in dry bean genotypes from Romania. J Hortic For Biotechnol. 2013;17:380-5.
30. Rebello CJ, Greenway FL, Finley JW. A review of the nutritional value of legumes and their effects on obesity and its related co-morbidities. Obes Rev. 2014;15(5):392-407. doi: 10.1111/obr.12144, PMID 24433379.
31. Du W, Jia X, Jiang H, Wang Y, li l, Zhang B. Consumption of dried legume and legume products among adults aged 18-59 y old in 15 provinces in China in 2015. Acta Nutrimenta Sin. 2018;40:17-22.
32. Yao Y, Hu Y, Zhu Y, Gao Y, Ren G. Comparisons of phaseolin type and α-amylase inhibitor in common bean (*Phaseolus vulgaris l*.) in China. The Crop Journal. 2016;4(1):68-72. doi: 10.1016/j.cj.2015.09.002.
33. Nciri N, Cho N. New research highlights: impact of chronic ingestion of white kidney beans (Phaseolus vulgaris L. var. Beldia) on small-intestinal disaccharidase activity in Wistar rats. Toxicol Rep. 2018;5:46-55. doi: 10.1016/j.toxrep.2017.12.016, PMID 29270365.
34. Thompson HJ, McGinley JN, Neil ES, Brick MA. Beneficial effects of common bean on adiposity and lipid metabolism. Nutrients. 2017;9(9):998. doi: 10.3390/nu9090998, PMID 28891931.
35. Lüthi C, Alvarez Alfageme F, Li Y, Naranjo SE, Higgins TJ, Romeis J. Potential of the bean α-amylase inhibitor α AI -1 to inhibit α-amylase activity in true bugs (Hemiptera). J Applied Entomology. 2015;139(3):192-200. doi: 10.1111/jen.12146.
36. Yang CH, Chiang MT. Effects of white kidney bean extracts on carbohydrate and lipid metabolism in rats fed a high-fat diet. Taiwan J Agric Chem Food Sci. 2014;52:154-62.
37. Thom E. A randomized, double-blind, placebo-controlled trial of a new weight-reducing agent of natural origin. J Int Med Res. 2000;28(5):229-33. doi: 10.1177/147323000002800505, PMID 11092233.
38. Boivin M, Zinsmeister AR, Go VL, DiMagno EP. Effect of a purified amylase inhibitor on carbohydrate metabolism after a mixed meal in healthy humans. Mayo Clin Proc. 1987;62(4):249-55. doi: 10.1016/s0025-6196(12)61900-4, PMID 2436011.
39. Boivin M, Flourie B, Rizza RA, Go VL, DiMagno EP. Gastrointestinal and metabolic effects of amylase inhibition in diabetics. Gastroenterology. 1988;94(2):387-94. doi: 10.1016/0016-5085(88)90426-x, PMID 2446948.
40. Harikumar KB, Jesil AM, Sabu MC, Kuttan R. A preliminary assessment of the acute and subchronic toxicity profile of phase2: an alpha-amylase inhibitor. Int J Toxicol. 2005;24(2):95-102. doi: 10.1080/10915810590936364, PMID 16036768.
41. Abdelrazeg S, Hussin H, Salih M. Propolis composition and applications in medicine and health. Int Med J. 2020;25:1505-42.
42. Sforcin JM. Biological properties and therapeutic applications of propolis. Phytother Res. 2016;30(6):894-905. doi: 10.1002/ptr.5605, PMID 26988443.
43. Hori JI, Zamboni DS, Carrao DB, Goldman GH, Berretta AA. The inhibition of inflammasome by Brazilian propolis (EPP-AF). Evid Based Complement Alternat Med. 2013;2013:418508. doi: 10.1155/2013/418508, PMID 23690844.
44. Resa PN, Nathaacute lia UF, Edna AB, Bruno AR, Mirela MO, Resa AB. Methodologies for the evaluation of the antibacterial activity of propolis. Afr J Microbiol Res. 2013;7(20):2344-50. doi: 10.5897/AJMR12.2362.
45. Rocha BA, Bueno PC, Vaz MM, Nascimento AP, Ferreira NU, Moreno P. Evaluation of a propolis water extract using a reliable RP-HPLC methodology and *in vitro* and *in vivo* efficacy and safety characterisation. Evid Based Complement Alternat Med. 2013;2013:670451. doi: 10.1155/2013/670451, PMID 23710228.
46. Tsuda T, Kumazawa S. Propolis: chemical constituents, plant origin, and possible role in the prevention and treatment of

obesity and diabetes. J Agric Food Chem. 2021;69(51):15484-94. doi: 10.1021/acs.jafc.1c06194, PMID 34910481.

47. Bankova V, Popova M, Trusheva B. The phytochemistry of the honeybee. Phytochemistry. 2018;155:1-11. doi: 10.1016/j.phytochem.2018.07.007, PMID 30053651.
48. Abdl El Hady FK, Hegazi AG. Gas chromatography-mass spectrometry (GC/MS) study of the Egyptian propolis 1-aliphatic, phenolic acids and their esters. J Appl Sci. 1994;9:749-60.
49. Balica G, Vostinaru O, Stefanescu C, Mogosan C, Iaru I, Cristina A. Potential role of propolis in the prevention and treatment of metabolic diseases. Plants (Basel). 2021;10(5):883. doi: 10.3390/plants10050883, PMID 33925692.
50. Natsir R, Usman AN, Ardyansyah BD, Fendi F. Propolis and honey trigona decrease leptin levels of central obesity patients. Enfermeria Clinica. 2020;30:96-9. doi: 10.1016/j.enfcli.2019.07.043.
51. Chen LH, Chien YW, Chang ML, Hou CC, Chan CH, Tang HW. Taiwanese green propolis ethanol extract delays the progression of type 2 diabetes mellitus in rats treated with streptozotocin/high-fat diet. Nutrients. 2018;10(4):503. doi: 10.3390/nu10040503, PMID 29670038.
52. Han X, Guo J, You Y, Zhan J, Huang W. P-Coumaric acid prevents obesity via activating thermogenesis in brown adipose tissue mediated by mTORC1-RPS6. FASEB J. 2020;34(6):7810-24. doi: 10.1096/fj.202000333R, PMID 32350925.
53. Boisard S, le Ray AM, Gatto J, Aumond MC, Blanchard P, Derbre S. Chemical composition, antioxidant and anti-AGEs activities of a french poplar type propolis. J Agric Food Chem. 2014;62(6):1344-51. doi: 10.1021/jf4053397, PMID 24443994.
54. Nie J, Chang Y, Li Y, Zhou Y, Qin J, Sun Z. Caffeic acid phenethyl Ester (Propolis extract) ameliorates insulin resistance by inhibiting JNK and NF-κB inflammatory pathways in diabetic mice and HepG2 cell models. J Agric Food Chem. 2017;65(41):9041-53. doi: 10.1021/acs.jafc.7b02880, PMID 28799756.
55. Shin SH, Seo SG, Min S, Yang H, lee E, Son JE, Kwon JY, Yue S, Chung MY, Kim KH, Cheng JX, lee HJ, lee KW. Caffeic acid phenethyl ester, major component of propolis, suppresses high-fat diet-induced obesity through inhibiting adipogenesis at the mitotic clonal expansion stage. J Agric Food Chem. 2014;62:4306-12.
56. Xu J, Ge J, He X, Sheng Y, Zheng S, Zhang C. Caffeic acid reduces body weight by regulating gut microbiota in diet-induced-obese mice. J Funct Foods. 2020;74:104061. doi: 10.1016/j.jff.2020.104061.
57. Liao CC, Ou TT, Wu CH, Wang CJ. Prevention of diet-induced hyperlipidemia and obesity by caffeic acid in C57BL/6 mice through regulation of hepatic lipogenesis gene expression. J Agric Food Chem. 2013;61(46):11082-8. doi: 10.1021/jf4026647, PMID 24156384.
58. Cardinault N, Tourniaire F, Astier J, Couturier C, Bonnet L, Seipelt E. Botanic origin of propolis extract powder drives contrasted impact on diabesity in high-fat-fed mice. Antioxidants (Basel). 2021;10(3):411. doi: 10.3390/antiox10030411, PMID 33803136.
59. Fei N, Zhao L. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germ-free mice. ISME J. 2013;7(4):880-4. doi: 10.1038/ismej.2012.153, PMID 23235292.
60. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500(7464):541-6. doi: 10.1038/nature12506, PMID 23985870.
61. Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BA. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016;535(7612):376-81. doi: 10.1038/nature18646, PMID 27409811.
62. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 2012;489(7415):242-9. doi: 10.1038/nature11552, PMID 22972297.
63. Roquetto AR, Monteiro NE, Moura CS, Toreti VC, de Pace F, Santos AD. Green propolis modulates gut microbiota, reduces endotoxemia and expression of TLR4 pathway in mice fed a high-fat diet. Food Res Int. 2015;76(3):796-803. doi: 10.1016/j.foodres.2015.07.026, PMID 28455065.
64. Cai W, Xu J, Li G, liu T, Guo X, Wang H. Ethanol extract of propolis prevents high-fat diet-induced insulin resistance and obesity in association with modulation of gut microbiota in mice. Food Res Int. 2020;130:108939. doi: 10.1016/j.foodres.2019.108939, PMID 32156386.
65. Drake TC, Rudser KD, Seaquist ER, Saeed A. Chromium infusion in hospitalized patients with severe insulin resistance: a retrospective analysis. Endocr Pract. 2012;18(3):394-8. doi: 10.4158/EP11243.OR, PMID 22297054.
66. Kaats GR, Blum K, Fisher JA, Adelman JA. Effects of chromium picolinate supplementation on body composition: a randomized, double-masked, placebo-controlled study. Curr Ther Res. 1996;57(10):747-56. doi: 10.1016/S0011-393X(96)80080-4.
67. Joseph LJ, Farrell PA, Davey SL, Evans WJ, Campbell WW. Effect of resistance training with or without chromium picolinate supplementation on glucose metabolism in older men and women. Metabolism. 1999;48(5):546-53. doi: 10.1016/s0026-0495(99)90048-3, PMID 10337851.
68. Aghdassi E, Arendt BM, Salit IE, Mohammed SS, Jalali P, Bondar H. In patients with HIV-infection, chromium supplementation improves insulin resistance and other metabolic abnormalities: a randomized, double-blind, placebo-controlled trial. Curr HIV Res. 2010;8(2):113-20. doi: 10.2174/157016210790442687, PMID 20163347.
69. Robati P, Mozafari H, Najarzadeh A, Dehghan A, Khorami E. The effect of chromium picolinate supplementation on body weight, body mass index and waist circumference in overweight and obese people. Med J Mashhad. 2015;58:117-22.
70. Jo H, AW. The effect of a new dietary mineral product on body composition and weight in overweight and obese people. The results from a comparative randomized 30d study. J Obes Eat Disord. 2016;2(1):496-507. doi: 10.21767/2471-8203.100015.
71. Vincent JB. Is the pharmacological mode of action of chromium(III) as a second messenger? Biol Trace Elem Res. 2015;166(1):7-12. doi: 10.1007/s12011-015-0231-9, PMID 25595680.
72. Wang ZQ, Qin J, Martin J, Zhang XH, Sereda O, Anderson RA. Phenotype of subjects with type 2 diabetes mellitus may determine clinical response to chromium supplementation. Metabolism. 2007;56(12):1652-5. doi: 10.1016/j.metabol.2007.07.007, PMID 17998017.
73. Kalra EK. Nutraceutical definition and introduction. AAPS Pharm Sci. 2003;5(3):E25. doi: 10.1208/ps050325, PMID 14621960.
74. Nasri H, Baradaran A, Shirzad H, Rafieian Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. Int J Prev Med. 2014;5(12):1487-99. PMID 25709784.
75. McClements DJ, Zou L, Zhang R, Salvia Trujillo L, Kumosani T, Xiao H. Enhancing nutraceutical performance using excipient foods: designing food structures and compositions to increase bioavailability. Comp Rev Food Sci Food Safe. 2015;14(6):824-47. doi: 10.1111/1541-4337.12170.
76. Asghar A, Randhawa MA, Masood MM, Abdullah M, Irshad MA. Nutraceutical formulation strategies to enhance the bioavailability and efficiency: an overview. Role of materials science in food bioengineering. Elsevier; 2018. p. 329-52.
77. McClements DJ, Ozturk B. Utilization of nanotechnology to improve the handling, storage and biocompatibility of bioactive lipids in food applications. Foods. 2021;10:1-17.
78. Jones D, Caballero S, Davidov Pardo G. Bioavailability of nanotechnology-based bioactives and nutraceuticals. Adv Food Nutr Res. 2019;88:235-73. doi: 10.1016/bs.afnr.2019.02.014, PMID 31151725.
79. Pateiro M, Gomez B, Munekata PE, Barba FJ, Putnik P, Kovacevic DB. Food products nanoencapsulation of promising bioactive compounds to improve their absorption, stability, functionality and the appearance of the final food products. Molecules. 2021;26(6):1547. doi: 10.3390/molecules26061547, PMID 33799855.

80. Rehman A, Ahmad T, Aadil RM, Spotti MJ, Bakry AM, Khan IM. Pectin polymers as wall materials for the nano-encapsulation of bioactive compounds. Trends Food Sci Technol. 2019;90:35-46.
81. Jain A, Ranjan S, Dasgupta N, Ramalingam C. Nanomaterials in food and agriculture: an overview on their safety concerns and regulatory issues. Crit Rev Food Sci Nutr. 2018;58(2):297-317. doi: 10.1080/10408398.2016.1160363, PMID 27052385.
82. Higashisaka K, Nagano K, Yoshioka Y, Tsutsumi Y. Nano-safety research: examining the associations among the biological effects of nanoparticles and their physicochemical properties and kinetics. Biol Pharm Bull. 2017;40(3):243-8. doi: 10.1248/bpb.b16-00854, PMID 28250267.
83. Zhang H, Jiang X, Cao G, Zhang X, Croley TR, Wu X. Effects of noble metal nanoparticles on the hydroxyl radical scavenging ability of dietary antioxidants. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2018;36(2):84-97. doi: 10.1080/10590501.2018.1450194, PMID 29667503.
84. Zanella M, Ciappellano SG, Venturini M, Tedesco E, Manodori l, Benetti F. Nutraceuticals and nanotechnology. Diet Ing Suppl. 2015;26:26-31.
85. Xiao J, Cao Y, Huang Q. Edible nanoencapsulation vehicles for oral delivery of phytochemicals: a perspective paper. J Agric Food Chem. 2017;65(32):6727-35. doi: 10.1021/acs.jafc.7b02128, PMID 28737908.
86. Fathi M, Martin A, McClements DJ. Nanoencapsulation of food ingredients using carbohydrate-based delivery systems. Trends Food Sci Technol. 2014;39(1):18-39. doi: 10.1016/j.tifs.2014.06.007.
87. Samaranayaka AG, li-Chan EC. Food-derived peptidic antioxidants: a review of their production, assessment, and potential applications. J Funct Foods. 2011;3(4):229-54. doi: 10.1016/j.jff.2011.05.006.
88. Zhang R, Han Y, Xie W, liu F, Chen S. Advances in protein-based nanocarriers of bioactive compounds: from microscopic molecular principles to macroscopical structural and functional attributes. J Agric Food Chem. 2022;70(21):6354-67. doi: 10.1021/acs.jafc.2c01936, PMID 35603429.
89. Fathi M, Donsi F, McClements DJ. Protein-based delivery systems for the nanoencapsulation of food ingredients. Compr Rev Food Sci Food Saf. 2018;17(4):920-36. doi: 10.1111/1541-4337.12360, PMID 33350116.
90. Wan ZL, Guo J, Yang XQ. Plant protein-based delivery systems for bioactive ingredients in foods. Food Funct. 2015;6(9):2876-89. doi: 10.1039/c5fo00050e, PMID 26156251.
91. Assadpour E, Jafari SM. An overview of specialized equipment for nanoencapsulation of food ingredients. In: Nanoencapsulation of food ingredients by specialized equipment. Cambridge MA: Academic Press; 2019. p. 1-30.
92. Ahmed EM. Hydrogel: preparation, characterization, and applications: a review. J Adv Res. 2015;6(2):105-21. doi: 10.1016/j.jare.2013.07.006, PMID 25750745.
93. Ahmad U, Ali A, Khan MM, Siddiqui MA, Akhtar J, Ahmad FJ. Nanotechnology-based strategies for nutraceuticals: a review of current research development. Nano Sci Technol Int J. 2019;10(2):133-55. doi: 10.1615/NanoSciTechnolIntJ.2019030098.
94. Bhattacharya S, Paul B, Biswas GR. Development and evaluation of hydrogel of an anti-fungal drug. Int J Pharm Pharm Sci. 2023;15:29-33. doi: 10.22159/ijpps.2023v15i10.48728.
95. Singh D. Application of novel drug delivery system in enhancing the therapeutic potential of phytoconstituents. Asian J Pharm. 2015;9:4.
96. Ajazuddin S, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 2010;81(7):680-9. doi: 10.1016/j.fitote.2010.05.001, PMID 20471457.
97. Akhavan S, Assadpour E, Katouzian I, Jafari SM. Lipid nano scale cargos for the protection and delivery of food bioactive ingredients and nutraceuticals. Trends Food Sci Technol. 2018;74:132-46. doi: 10.1016/j.tifs.2018.02.001.
98. Mozafari MR, Flanagan J, Matia Merino L, Awati A, Omri A, Suntres ZE. Recent trends in the lipid-based nanoencapsulation of antioxidants and their role in foods. J Sci Food Agric. 2006;86(13):2038-45. doi: 10.1002/jsfa.2576.
99. Bozzuto G, Molinari A. Liposomes as nanomedical devices. Int J Nanomedicine. 2015;10:975-99. doi: 10.2147/IJN.S68861, PMID 25678787.
100. Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, labib GS. Nanocarrier drug delivery systems: characterization, limitations, future perspectives and implementation of artificial intelligence. Pharmaceutics. 2022;14(4):883. doi: 10.3390/pharmaceutics14040883, PMID 35456717.