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"Berberine" A Traditional Chinese Medicine (TCM): An Emerging Alternative In The Management Of Obesity

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Abstract
There is an awful need for a new obesity treatment, which is broadly described as aberrant or excessive fat accumulation that leads to a health risk. The difficulty has grown to epidemic proportions, with over four million human beings dying each year as a result of being overweight or obese. According to current trends, one in five adults worldwide is expected to be affected by obesity by 2025. It is estimated that by 2035, half of the world's population could be overweight. In recent times, reducing calorie intake and adopting intermittent fasting have emerged as widely popular approaches for managing weight. Pharmacotherapy, medical devices, and bariatric surgery are different treatment options for patients requiring additional interventions. The commonly prescribed anti-obesity medications are phentermine, orlistat, phentermine/topiramate extended-release, lorcaserin, naltrexone sustained-release (SR)/bupropion SR, liraglutide, and semaglutide. The adverse effects of these vary from mild to more serious, including rare but potentially severe side effects. The withdrawal of Conventional medicine, also known as allopathic medicine, such as Fenfluramine, Dexfenfluramine, Sibutramine, and Rimonabant from the market due to their potential adverse effects has raised reservations about the use of modern medicine in obesity. Present therapeutics of obesity in modern medicine are limited due to poor tolerability and low compliance owing to associated side effects, restricting their potential widespread use. Therefore, the development of additional drugs from natural sources is currently arousing considerable interest, as they are likely to have fewer side effects. The discovery of Artemisinin and the Nobel Prize awarded to Dr. Youyou Tu in 2015 for it introduced Traditional Chinese Medicine (TCM) to the world, and it further increased interest in investigating TCM compounds as a potential source of modern medicine with clear mechanisms and possible unwanted effects. Recently, an increasing number of clinical trials and systematic reviews (SRs) have been carried out and published, demonstrating that TCM appears to be effective in numerous diseases. To date, a variety of clinical trials of TCM for weight issues have been conducted and reported, yielding compelling findings. Berberine, a TCM with a wide range of pharmacological effects, including anti-inflammatory, antibacterial, glucose-lowering, lipid-lowering, and anticancer effects, is now widely available in the clinics of China as an over-the-counter (OTC) drug due to its wide source, high safety, and low cost. Extensive scientific research and clinical trials have revealed the therapeutic properties of Berberine, including its potential benefits in obesity management. However, its chemical structure limitation, poor water solubility, cytotoxicity, and low bioavailability throughout oral administration limit the scope of its clinical utility. Berberine derivatives, emerging more recently, have shown significant improvements in pharmacological activity compared to the parent berberine.

Keywords: *Obesity, Traditional Chinese medicine (TCM), Berberine*

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I. Introduction

Overweight and obesity are defined as the excess of body fat or adipose tissue (AT) resulting from excessive intake of nutrients and/or decreased energy expenditure and remains a continuing global health concern, as it is associated with increased risk of numerous chronic diseases, including type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD).[1-3] Body mass index (BMI) (weight in kg/height in m2), the most widely used formula to define overweight (BMI 25 to29.9 kg/m2) and obesity (BMI 30 kg/m2), while not being an authentic measure of adiposity, is simple to use in health screenings and epidemiological surveys. According to the World Health Organization (WHO), the prevalence of obesity nearly tripled between 1975 and 2016. [4-6] In

June 2013, the American Medical Association officially considered obesity as a disease. The World Obesity Federation estimates that by 2020, around 770 million adults globally will have been affected by obesity. It is also estimated that more than 1 billion human beings will be obese by the year 2030 worldwide if they do not act soon. Obesity has emerged as one of the prime public health problems facing the world today. Therefore, obesity has become a primary challenge for the entire society. Reducing body weight with the aid of lifestyle alteration is advisable, but every so often, drug intervention is necessary. [7-11]

However, the weight loss drugs prescribed in modern medicine result in many unfavorable reactions. For example, Fenfluramine and dexfenfluramine were withdrawn from the market in 1997 due to their possible detrimental effects on heart valves, and sibutramine was withdrawn in 2010 because of an increased risk of heart attacks and strokes in the U.S. Additionally, rimonabant was withdrawn from Europe in 2009. [12-16] Surgery is commonly used in morbidly obese patients (BMI ≥ 40 kg/m2) or patients with comorbidities such as hypertension, diabetes, and obstructive sleep apnea. Common surgical complications consist of infection, postoperative anastomotic fistula, deep vein thrombosis, and long-term issues such as anemia and malnutrition. Given the risks of obesity and the shortcomings of modern medicine, alternative treatments ought to be similarly investigated. The availability, cost, and unfavorable consequences of conventional modern medicinal drug treatment limit effective therapeutics for obesity. [17-21] Thus, due to the limitations and concerns with currently accessible modern treatments, some people, especially in Asia, have turned to complementary and alternative medicinal drugs (CAM), inclusive of traditional Chinese medicine (TCM), for weight reduction and its related symptoms in searching for a treatment modality with possible efficacy and few adverse effects (AEs) both in developed and developing nations. As one vital component of TCM, Chinese herbal medicine (CHM) is broadly used in Southeast Asia, such as Japan, South Korea, Malaysia, and Vietnam, with a 3,000-year-old history. [22-24] Artemisinin, for the treatment of uncomplicated Plasmodium falciparum malaria, was the most successful TCM compound to be acknowledged in the world. Dr. Youyou Tu was awarded the Nobel Prize for Medicine in 2015 for its discovery. Artemisinin has led the world to discover an additional cure for a remarkable disease found in Chinese medicinal herbs. [25-28] Extensive preclinical and clinical research has highlighted the pharmaceuticals making use of TCM as antidiabetics, antihyperlipidemics, antiobesity, anti-inflammatories, and antioxidants. The use of herbal medicinal drugs to deal with weight problems is currently garnering tons of attention. Recently, an increasing number of clinical trials and systematic reviews (SRs) have been conducted and published, demonstrating that Chinese herbal medicine appears to be effective in weight reduction. To date, numerous clinical trials of TCM for obesity have been conducted and reported, yielding constructive findings. During the previous decade, an awful lot of the latest developments have been made in finding out about weight loss therapy with herbal medicinal drugs. Clinical investigations of TCM are effective in the treatment of obesity, and animal experiments have begun to reveal the potential mechanisms of various herbal medicines. Studies have additionally revealed that Chinese herbal remedies for obesity produce fewer adverse reactions than conventional chemical agents, and their safety profile is acceptable. [29-35] Berberine (BBR) has a molecular formula of C20H18NO4 and belongs to the class of isoquinoline alkaloids. In nature, it mainly exists in Chinese herbal medicine plants such as Rhizoma Coptidis. Due to its remarkable anti-inflammatory and antibacterial effects, it is widely used clinically to treat diarrhea and intestinal inflammatory diseases. Berberine exhibits a wide range of pharmacological effects, including anti-inflammatory, antibacterial, glucose-lowering, lipid-lowering, and anticancer properties. It is now widely available in Chinese clinics as an over-the-counter (OTC) drug due to its wide availability, high safety, and low cost. In addition to the functions described, it can also be used to treat metabolic diseases such as diabetes, hyperlipidemia, atherosclerosis, and other cardiovascular diseases. However, its chemical structure limitation, poor water solubility, and low bioavailability throughout oral administration limit the scope of its clinical utility. [36-40]

We have previously discussed Obesity, Its Pathophysiology, and management, including bariatric surgery and Anti-Obesity pharmacotherapy, in our article**.** [41] In this article, based on an intensive literature review, we discuss the natural compounds of traditional Chinese medicine as potential alternatives in the management of obesity, exploring a variety of Chinese herbs and traditional Chinese medicine (TCM) approaches known to support weight management. The literature search in this study is sourced from PubMed, Google Scholar, and Research for Life using searches that contained the following keywords: "Obesity," "Berberine," "Traditional Chinese Medicine," and "Chinese Herbal Medicine "in peer-reviewed, open-access articles, published from 2000 to 2024 is included in the study.

Traditional Chinese Medicine (TCM) In Obesity

Traditional Chinese medicine (TCM) are the therapies and products made from any part of medicinal plants (e.g., leaves and roots) and some non-herb-based components (e.g., shells and powdered fossil)— has a history of more than 2500 years with a unique theory of prognosis, treatment, and is regarded a modality of complementary medication in Western countries. TCM has been increasingly used for a wide range of chronic diseases in China and elsewhere, in the form of raw plant materials, powders, capsules, tablets, and/or liquids.

TCM is a complex component constituted of mixed medicinal extracts from Chinese herbs and animals, and is prescribed based on the philosophical theory of Chinese medicine, for instance, the theories of "Yin Yang" and "Five Elements." Though mysterious and empirical, TCM has received front-line experience in combating diseases for millennia in Chinese history with effectiveness and low side effects. Many TCM interventions have long been used for the treatment of diseases such as Type 2 diabetes, hypertension, and obesity. Huanglian and Gegen were the Chinese herbs included in the impaired glucose tolerance (IGT) focused trial. Similarly, Gauteng and Tianma were the most frequently used Chinese herbs in hypertension. Huanglian was the most common Chinese herb, followed by Ginseng, Shanzhuyu, Dahuang, and Huangqi to be used in diabetic focused trials. Green tea and Juemingzi were the Chinese herbs included in two Chinese herbal medicine formulas amongst the three obesity-focused trials. All Chinese herbal products showed a greater decrease in body weight than placebos after treatment. All hyperlipidemia-focused research reported safety-related information and mentioned no deaths. Three trials specified their side effects in the Chinese herbal medicine intervention groups, including heartburn/flatulence, diarrhea, and stomach upset. It is noteworthy that Monascus purpureus rice preparation (Xuezhi-Kang capsule in Chinese), of which the main ingredient is red yeast rice, was tested in four hyperlipidemia-focused Randomized Controlled Trials (RCTs), and was found to have a more significant decrease of TC and LDL-C, including lifestyle intervention. However, there was no significant improvement in TC or LDL-C amongst those receiving the red yeast rice product alone compared to placebo. Peng et al reported the effectiveness of Chinese herbal medicine in obesity, containing the main constituents as Danshen , Juemingzi , Ze Xie , and/or Shanzha . They found a decrease in TC, LDL-C, and/or TG levels compared to control interventions. [25,42-45]

Fortunately, nowadays, high-level isolation techniques have enabled scientists to identify active components from TCM to reveal the molecular mechanisms of their therapeutic effects, thus promoting the re-discovery of ancient TCM compounds to be potentially advanced as drugs under the Western medical standard. A few promising TCM compounds with successful implications include, but are not limited to, artemisinin in treating malaria and arsenic trioxide in acute promyelocytic leukemia, with more waiting to be added to the list. Additionally, the studies on TCM open a new therapeutic avenue and show great potential in the combat against obesity, though challenges exist. Chinese herbal medicine has shown the potent capability of improving both obesity and its metabolic diseases through the regulation of gut microbiota. Shuqing Gong et al outlined that traditional herbal formula Kang Shuai Lao Pian (KSLP) is a promising traditional Chinese medicine (TCM) applicable for individuals with high-fat diet (HFD) habits. [47] Chang et al. reported that the therapeutic effect of Ganoderma lucidum against HFD-induced obesity works through the compositional regulation of gut microbiota. Substantial data demonstrate the effectiveness and low adverse effects of six key candidates, including artemisinin, curcumin, Celastrol, capsaicin, berberine, and ginsenosides, to review their recent discoveries in the metabolic field, with special focus on their therapeutic efficacy and molecular mechanisms in treating obesity and metabolic diseases, promoting a few into pre-clinical or clinical trials, though not all trials gave consistent results**.**[48] For example, Lee et al found that artemisinin acid and artesunate inhibit the development and differentiation of adipocytes by suppressing master regulators C/EBPs and PPARγ in adipogenesis. [49] Jang Lu et al have identified artemether, an artemisinin derivative, as an activator of browning and thermogenesis in vitro. Further examination reveals that artemisinin and other artemisinin derivatives, dihydroartemisinin, and artesunate could also promote browning. [50] Curcumin has produced controversial results, which call for more randomized, double-blind, parallel controlled, multi-center clinical trials for fair judgment before it can be put into use. Celastrol, capsaicin, and berberine are all ensuring innovative therapeutics against obesity and metabolic diseases for their considerable effectiveness on metabolic improvement from in vitro and in vivo studies. Clinical data is required to assess their efficacy and side effects on patients in the future. Ginseng, though famous for its universal effects, has to be sensibly scrutinized to identify the detailed functions of individual ginsenosides in metabolism. [50-53] Fan Wu et al. found that Wu-Mei-Wan is effective in preventing obesity; the potential mechanism is associated with reducing white adipose tissue and enhancing brown adipose tissue function. [54] An appropriate quantity of TCM has shown promising consequences in the treatment of obesity. A few of them are in clinical trials, and some are OTC medicines in China. Though TCM has proven utmost outcomes in therapeutics, its adverse effects and long-term use need further investigation. Some of the TCMs with anti-obesity effects in the animal model are listed in the table.

Table 1: Summary of Anti-obesity effects of TCM in animal module

TCM/Herb	Component	Animal	Effects
Rhizoma coptidis	Berberine	Mice	Visceral adipose↓ Weight↓ Blood glucose↓ Lipid levels↓
Panax ginseng C. A. Mey	Ginsenoside Rg1 Ginsenoside Rb1 Ginsenoside Rg3	Mice	Bodyweight↓ Food intake↓ Blood glucose↓

TCM/Herb	Component	Animal	Effects
			TC↓ TG↓
Radix Lithospermi	Acetylshikonin; shikonin	Rat	Bodyweight↓ FFA↓ TG↓ inhibited Differentiation Fat accumulation, Food intake↓
Ephedra sinica Stapf.	Ephedra	Male ICR mice	Bodyweight ↓ Fasting glucose↓ HDL-C↑
Rheum palmatum L.	Chrysophanic acid	Mice	Bodyweight↓ TG↓ HDL-↑, TC↓ Food intake↓
Green tea	Catechin	Mice	Bodyweight↓ Energy intake HOMA-IR↓, TG ↓, TC↓ FFA↓
Astragalus membranaceus (Fisch.) Bunge	Astragalosides I Astragalosides II	Mice	Body weight ↓ Food intake ↓ HDL-C↑
Carthamus tinctorius L	Saffron, crocin	Rat	Food intake, relative liver weight
Ganoderma lucidum (Leyss. ex Fr.) Karst	Saffron	Mice	Inflammation endotoxemia ↓ Insulin resistance ↓ Regulated lipogenic gene expression.
Tripterygium wilfordii Hook. f	Celastrol	Mice	HFD: food intake ↓ Energy expenditure ↑ Bodyweight↓ db/db or ob/ob mice: body weights, lean mass, and fat the percentage was not affected

*__HOMA-IR__: Homeostatic Model Assessment of Insulin Resistance; **HDL-C-High-density lipoprotein cholesterol; LDL-C-Low-density lipoprotein cholesterol; LDLR-Low-density lipoprotein receptor; TC-Total cholesterol; TG-Triglyceride**

Berberine (BBR)

Berberine, a TCM compound, is a quaternary ammonium salt from the group of isoquinoline alkaloids (2,3 methylenedioxy-9,10-dimethoxyprotoberberine chloride; (C 20 H 18 NO 4) with a molar mass of 336.36122 g/mol. It is found in plants as Berberis [e.g., Berberisaquifolium (Oregon grape), Berberis vulgaris (barberry), Berberis aristata (tree turmeric)], Hydrastis Canadensis (goldenseal), Xanthorhiza simplicissima (yellowroot), Phellodendron amurense (Amur cork tree), Coptis Chinensis (Chinese goldthread), Tinospora cordifolia, Argemone mexicana (prickly poppy), and Eschscholzia californica (Californian poppy). [55] Berberine is a yellow, odorless powder and has a characteristic alkaloid bitterness. Regarding the solubility of berberine in the different solvents, it is sparingly soluble in water, slightly soluble in ethanol or methanol; however, the salt form is relatively water-soluble. The chloride or sulfate salt of BBR is usually used for clinical purposes. The yellow coloration of berberine is responsible for the yellow or gold appearance of its source plant. [56-60]

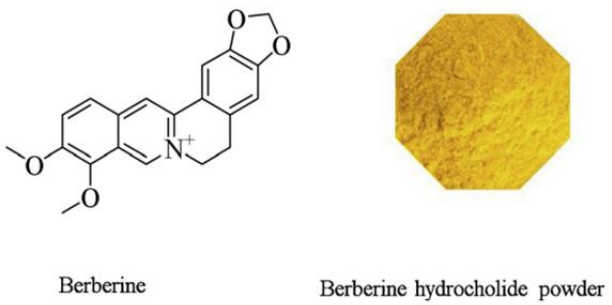

Figure 1: Structure and Color of Berberine [60]

Berberine was first isolated from H. Canadensis (goldenseal) as a chemical compound in 1917. Initially, Berberis species were used to dye wool, leather, and wood (e.g., the textile industry) due to their deep yellow and yellow fluorescent characteristics. Its medicinal use was also dated for hundreds of years as a lively principle for varied medicinal plants, which are still in use so far, including as ingredients of varied food supplements. Berberine-containing plants such as Berberis vulgaris, are used medicinally in nearly all traditional medical systems and have a history of usage in Ayurveda, Iranian and Chinese medicine for at least 3000 years. [56] Ancient Egyptians used barberry fruit with fennel seeds to keep off pestilent fevers. Indian Ayurveda physicians used barberry for the treatment of dysentery and traditional Iranian medicine as well as uses its fruit as a sedative. In Northern Europe, barberry was wont to treat gall bladder and liver problems, while it had been utilized in the treatment of abnormal uterine bleeds and rheumatism in Russia and Bulgaria. In North America, the Eclectics used barberry for the treatment of malaria and as a general tonic. Also, the American Indians found it effective in improving appetite and used its dried fruit as a gargle. [56,58,60-62]

Berberine was used in Chinese and Ayurvedic medicine as early as 3000 BC. The European barberry (Berberis vulgaris) was used as an herbal medicine to treat diarrhea and dysentery. Its constituents were then extracted, among which berberine was the most active alkaloid. BBR is also the principal bioactive ingredient of Rhizoma coptidis (also named 'Huang Lian' in Chinese), a common traditional Chinese medicinal herb used for the therapy of inflammatory disorders and diabetes mellitus (DM). The earliest record of the use of Rhizoma coptidis as a medication dates back to A.D. 200 in the book of 'Shen Nong Ben Cao Jing'. For the first time, the anti-diabetic effect of Rhizoma coptidis was documented in the "Note of Elite Physicians" by Hongjing Tao approximately 1,500 years ago. [55,59,63-67]

Berberine has been used as a non-prescription drug in clinics for diarrhea, dysentery, stomatitis, and hepatitis. [67] A relatively large number of clinical studies have shown that Berberine can exhibit therapeutic activities in the treatment of various diseases, including diabetes, hyperlipidemia, cancer, hypertension, stroke, metabolic syndrome, polycystic ovary syndrome, and liver disease, in human subjects. Numerous studies have been carried out to unravel its other pharmacological and therapeutic effects, primarily on T2DM, lipid metabolism, and tumors. [68] It has shown some effects as anti-aging too, for example, Halicka et al. noted that Berberine also exerts anti-aging function by mechanisms inhibiting the mTOR/S6 pathway via AMPK activation, as well as reducing the endogenous ROS level and constitutive oxidative DNA damages through NRF2. Navrotskaya et al stated, In Drosophila melanogaster, Berberine prolongs life span and stimulates locomotor activity potentially by blocking kynurenine formation from tryptophan, which is associated with aging. Canaanet al. mentioned that since it has been shown that metabolic improvements are one of the major drives for longevity, it would be interesting to assess how much of the extended longevity is contributed by Berberine's promotion of metabolic health in the future and whether mammalian lifespan is also affected by Berberine treatment. Furthermore, ongoing experimental and clinical studies have illuminated the great potential of Berberine in the regulation of glucose and lipid homeostasis, cancer growth, and inflammation. In preclinical models, Berberine demonstrates that it affects gut microbiota by reducing the diversity of microbes starting at a dosage of 100 mg/kg/day. [60] Moreover, in animal models, Berberine has an effect on glucose by inhibiting α-glycosidase at a dose of 200 mg/kg/day. Berberine is also known to be effective against the differentiation of adipocytes through a decrease in LXRs, PPARs, and SREBPs expression at 150mg/kg/day. Other mechanisms ascribed to Berberine are related to its inhibition of hepatic gluconeogenesis through the Phosphoenolpyruvate carboxy kinase (PEPCK), Glucose-6-phosphate (G6Pase), and AMP-activated protein kinase (AMPK). Furthermore, Berberine (associated with Red Yeast Rice) is effective in decreasing lipid levels in rats, which consequently lowers the risk of weight gain at the dosage of 40 mg/kg to 380 mg/kg/day. All the above preclinical data are confirmed in human studies, where Berberine can modulate the diversity of gut microbes at a dose of 500 mg/day. [62,68] Additionally, Berberine has been found to have a beneficial impact on gene regulation for cholesterol absorption at a daily dose of 300 mg in humans. A daily dose of 1.0 g also showed amelioration of glucose accumulation. Furthermore, the lipid-lowering effect of Berberine is comparable to that of conventional lipid drugs but with low toxicity. Even in humans, its lipid-lowering and insulin-resistance improving actions have been demonstrated in numerous randomized clinical trials. Therefore, it is the right time to transform the beneficial effects of Berberine into therapeutic practice. [55,59,62,69-71]

Berberine in Dyslipidemia

Berberine regulates lipid metabolism by upregulating hepatic low-density lipoprotein (LDL) receptors through the AMPK-dependent Raf-1 activation pathway. The effect of berberine on obese mice demonstrated that berberine administered through the peripheral or central route can lower liver weight, hepatic and plasma triglycerides (TGs), and cholesterol contents by promoting AMPK activity and fatty acid oxidation and modulation of expression of genes involved in lipid metabolism. A recent meta-analysis of randomized clinical trials confirmed the cholesterol and triglyceride-lowering effect of berberine. The lipid-lowering activity of berberine, in association with other nutraceuticals, has also been clearly confirmed in a relatively large number of

randomized clinical trials. BBR lowered lipid levels via competitive inhibition of HMG-CoA reductase, and by interacting with the 3 ′-UTR of the LDL receptor (LDLR) to improve the stability of LDLR mRNA. An in vivo experiment showed that BBR alleviated nonalcoholic fatty liver by activating SIRT3.In foam cells, BBR promoted cholesterol efflux by increasing ROS production and induced autophagy by inhibiting mTOR and Akt phosphorylation. The supposed mechanism of action is the increased expression of the liver receptor for LDL mediated by the inhibition of the Proprotein-convertase-subtilisin-Kexin-9 (PCSK9) activity. Alongside the upregulation effect of berberine on the LDL receptor, it could also reduce triglycerides by AMP kinase activation and MAPK/ERK pathway blocking. [62,68,71]

A study performed by Wang et al. concluded that Berberine decreases the cholesterol uptake through Caco-2 cells and permeability through Caco-2 monolayer through the downregulation of Acyl-coenzyme A: cholesterol acyltransferase-2 expression. Chow et al. showed that 11 different types of proto-Berberine regulate specific genes of 3T3-L1 adipocytes in mice. It was deduced that Berberine down-regulates different transcriptional factors, PPARγ and C/EBPα. Downregulation leads to the switching off of genes, causing a lowering of the lipid profile. Jiang's group has found that Berberine binds to the 3' UTR of LDLR mRNA, resulting in increased LDLR stability, enhanced hepatic LDL assimilation, and reduced cholesterol level. [84] Kong et al reported that in hypercholesterolemic patients and hyperlipidemic hamsters, berberine treatment significantly lowers total cholesterol, LDL, and triglyceride levels with a mechanism of action distinct from Statins, a classic cholesterol-lowering drug targeting HMG-CoA reductase. Later, Ning's group showed the effectiveness of Berberine in lipid and glycemic control in a larger cohort of patients with Type 2 diabetes and hyperlipidemia based on comprehensive metabolomics. [87,88] Kong et al. have described BBR as "a new lipid-lowering drug" after observing its efficacy in lowering lipid levels in vitro and in vivo, which was comparable to that of statins. [89] BBR also lowered lipid levels via competitive inhibition of HMG-CoA reductase, and by interacting with the 3 ′ -UTR of the LDL receptor (LDLR) to improve the stability of LDLR mRNA. Alongside the upregulation effect of berberine on the LDL receptor, it could also reduce triglycerides by AMP kinase activation and blocking the MAPK/ERK pathway. [92-96]

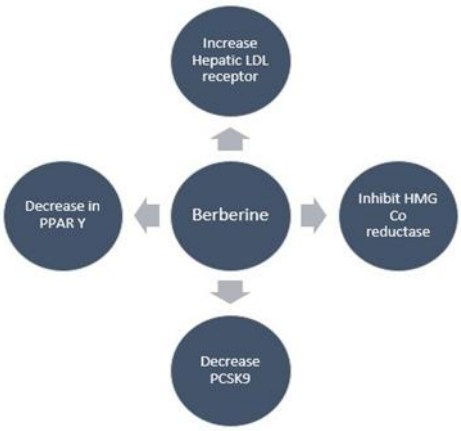

Figure 2: Hypolipidemic Mode of Action of Berberine

Berberine in Obesity

The anti-obesity potential of Berberine has been demonstrated in numerous experimental models. Through the AMP-Activated Protein Kinase (AMPK)-dependent and independent mechanisms, Berberine can inhibit adipogenesis in experimental animals. Some of the effects of Berberine in obesity could be linked to its ability to modulate microRNA (miRNA) as shown from its inhibitory effect on 3T3L1 adipocytes cell differentiation and reduction of TGs contents via increased mRNA expression levels of miRNA-27a and miRNA-27 b. This, in turn, is linked to the negative regulation of the peroxisome proliferator-activated receptors (PPAR)-γ by these miRNAs (miRNA-27a). Adipocyte differentiation has also been widely reported as a mechanism for the anti-obesity effect of Berberine through various distinct mechanisms, including suppression of galectin-3 in mouse primary adipocytes isolated from epididymal white adipose tissues. It also suppresses the cAMP-response element-binding protein (CREB)phosphorylation and CCAAT enhancer-binding protein-β(C/EBPβ) expression at the early stage of 3T3-L1 preadipocyte differentiation. In addition, Berberine could enhance thermogenesis in white adipose tissues. [62,63,66,68,70]

The studies found that Rhizoma coptidis can reduce weight, lower lipids, reduce lipid synthesis, and inhibit adipogenesis. Xie et al. found that Rhizoma coptidis (RC) (200 mg/kg) and Berberine (200 mg/kg) significantly lowered body and visceral adipose weight, reduced blood glucose and lipid levels, and decreased

degradation of dietary polysaccharides in high-fat diet (HFD)mice. Both the ex vivo and in vitro trials confirmed that RC and Berberine can regulate gut microbes to reduce weight. It is based on the plethora of shreds of evidence for Berberine as a weight, lipid, and cholesterol-lowering agent, whose mechanism is through modulation of the gut microbiota**.** [72,73] Recent studies by Liu et al. on rats and Tian et al on mice concluded that Berberine alters bacterial physiology, community composition, and increases the growth of protective bacteria like Bifidobacterium. It is affected by the inhibition of LPS-induced TLR4/TNF-α activation and BSH expression. [74] Berberine could potentially promote metabolic health by playing a role in the microbiota-gut-brain axis. Zhang et al. stated that Berberine treatment causes a structural change in gut microbial flora, vastly reducing its diversity by enriching a few short-chain fatty acid (SCFA)- producing bacteria, including Blautia and Allobaculum. In turn, this elevates SCFA levels in the intestine and alleviates host inflammation. [75,76] Li et al. stated that administration of ginseng (0.5 g/kg diet) to HFD-induced obese mice for 15 weeks significantly decreased body fat mass gain, improved glucose tolerance, and insulin sensitivity, and prevented hypertension. [77] Lee et al found artemisinic acid and artesunate are found to inhibit the development and differentiation of adipocytes by suppressing master regulators C/EBPs and PPARγ in adipogenesis. [78] Jang Lu et al have identified artemether, an artemisinin derivative, as an activator of browning and thermogenesis in vitro. Studies have suggested Celastrol, capsaicin, and berberine are all promising novel therapeutics against obesity and metabolic diseases for their convincing effectiveness on metabolic improvement from in vitro and in vivo studies. [79] Fan Wu et al found Wu-Mei-Wan is effective in preventing obesity, the potential mechanism is associated with reducing white adipose tissue and enhancing brown adipose tissue function. [80] A study done on human fat in vitro and by Yang et al. showed that the expression of PPARγ2, C/EBPα, adiponectin, and leptin mRNA is downregulated in preadipocytes upon treatment with Berberine**.** [83] Furthermore, Zhang et al stated that Berberine is shown to activate thermogenesis in adipocytes through the AMPK-PGC1α axis, which leads to increased energy expenditure, reduced weight gain, and improved cold tolerance in obese db/db mice**.** [85,86] Besides, Recent discoveries of basic, translational, and clinical studies have identified many novel molecular targets of BBR (such as AMPK, SIRT1, LDLR, PCSK9, and PTP1B) and provided novel evidence supporting the promising therapeutic potential of BBR**.** [87,88] One of the best researched experimental models for the anti-obesity effect of berberine is the high-fat diet-induced obesity in mice, where it has been shown to inhibit adipogenesis. The anti-obesity (weight loss), lipid-lowering effect of berberine as a function of TGs and cholesterol reduction has been demonstrated in both rats and humans. Through both central and peripheral action that are distinctly different from the statins, berberine is now known as a potent anti-obesity and lipid-lowering agent. Randomized clinical trials have demonstrated the lipid-lowering and anti-obesity actions of berberine in humans. [90,91]

Berberine is a potential drug to treat obesity by downregulation of adipogenesis and lipogenesis. This anti-obese activity is consistent with the finding that berberine significantly decreased the sizes and number of lipid droplets in 3T3-L1 adipocytes. The effect of berberine on mice was found to cause contracted adipocytes. BBR inhibits the expression of adipogenic enzymes (fatty acid synthase, acetyl-CoA carboxylase, acyl-CoA synthase, and lipoprotein lipase) and transcription factors (SREBP-1c, C/EBP, and PPAR-γ), thereby decreasing the production of adipocytes and the secretion of leptin. BBR strongly increases the expression of UCP1 and other classical BAT marker genes to facilitate energy expenditure and thermogenic activities in the BAT of obese db/db mice. Liu et al, Hwang et al, Zhang et al, Kim et al and many more studies suggest that berberine has an anti-obesity effect in animals and cell culture via inhibition of adipogenesis, Promotion of AMPK activity, and a decrease in the expression of PPAR γ and C/EBP α. Hu et al stated the anti-obesity action of berberine due to an increase in expression of GATA-2 and GATA-3, both at the gene and protein levels. Shang et al stated that due to the inhibition of IkB kinase β (ser 181). Whereas Teodoro et al found increasing mitochondria SirT3 activity, Spatuzza et al reported inhibition of pro-inflammatory IL-6 and TNF-alpha protein release, and Xie et al. suggested regulation of gut microbes is a possible mechanism of the anti-obesity effect of berberine in vitro and in vivo studies. [97-102] Further, Sun et al found that Berberine increases serum Glucagon-like peptide-1 (GLP-1) and Neuropeptide Y level while decreasing Orexin A level, which are all gut-brain peptides critical in satiety and energy homeostasis. Also, Sun et al. noted the GLP1 receptor is found to be elevated in the hypothalamus of berberine-treated mice, suggesting the central nervous system might be another target for metabolic regulation by Berberine. [80,81]

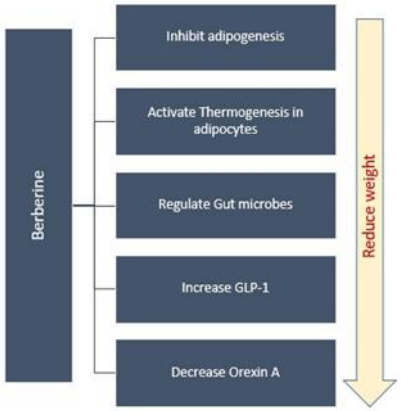

Figure 3: Mode of action of Berberine in Obesity

Adverse Effects, Interactions, And Limitations Of Berberine

Research in animal, human, and clinical trials indicates that Berberine (BBR) is generally safe at conventional doses, with a relatively low incidence of adverse reactions, such as gastrointestinal discomfort, and transient increases in plasma bilirubin levels. Even though BBR is relatively safer, it should be taken carefully to avoid adverse reactions in specific cases. For example, BBR has nearly 10 times greater effect compared to phenylbutazone in replacing bilirubin in binding to albumin, so any BBR-containing herbs should be avoided in pregnancy jaundice and infants. BBR interacts with macrolides, and it may lead to potentially dangerous arrhythmias. Berberine has strong interactions with statins; the combination increases cardiotoxicity by inhibiting CYP3A4 and human ether-a-go-go-related genes (hERG) potassium channels. Besides those adverse effects and drug-drug interactions, BBR can prevent toxic reactions too in different tissues caused by antitumor drugs such as cisplatin, cyclophosphamide, doxorubicin, and bleomycin, as well as side effects of analgesics (e.g., acetaminophen). Highly purified and concentrated berberine is safe; its Lethal Dose 50 (LD50) in mice is 25 mg/kg. [100,103,104]

Berberine is a cationic alkaloid. Pharmacokinetic data in rodents and humans have revealed that berberine is slightly soluble in water, has poor intestinal absorption (<5%), and undergoes rapid metabolism in the body, resulting in low oral bioavailability. For example, BBR is converted to an ionic form under physiological conditions and self-aggregates at low pH values. Self-aggregation of BBR reduces its solubility in the gastrointestinal tract and its ability to permeate the gut wall. [59] In addition to reduced permeability to the gut wall, P-glycoprotein (P-gp), located in the epithelial cell membrane, can actively efflux many drugs, actively expelling the alkaloid berberine from the lumen mucosal cells, thereby limiting their oral bioavailability. [105] The absolute bioavailability of berberine is far less than 1% given that even the absorbed berberine from the gut could be excreted back to the intestinal lumen through the action of P-glycoprotein. Chen et al. reported absolute bioavailability from the oral route in rats as 0.68 %, and as expected, inhibitors of P-glycoprotein could increase bioavailability from the intestine. [60] Berberine absorption in rats could also be improved by up to 6 times by P-glycoprotein inhibitors, suggesting the contribution of P-glycoprotein to the poor intestinal absorption of berberine. [60, 62] Absolute oral bioavailability in rats of 0.36 % has also been reported, making intestinal first-pass elimination of berberine the major barrier to its oral bioavailability. [106,107] With such a poor degree of absorption from the gut, berberine ingested in hamsters is largely accumulated in the gut (not the circulation), and its bioavailability through the intraperitoneal route was much better than the oral/Intragastric route. One of the emerging links between the expected poor bioavailability of berberine and its pharmacology is the gut microbiota that modulates both the pharmacokinetics profile and its biological effects. [59,60,62]

II. Discussion

The growing risk of weight problems to world health has prompted scientists and researchers to put greater effort into finding an efficient anti-obesity ingredient. Given the risks of weight problems and the shortcomings lengthy of western medicine, choice redress needs to be further investigated. With the growing attention of people's healthcare, drugs with herbal products as raw substances are progressively preferred by way of human beings all over the world for their special advantages in preventing and curing diseases, rehabilitation, and health care with minimal adverse effects. Thus, due to the limitations and issues with currently available western medicines treatments, some people came in search of complementary and alternative medicine. Numerous possible substances from natural sources have been investigated alongside their active components. Recently, several developments at the interface of natural product chemistry and medicine have demonstrated that various plant extracts have good anti-obesity properties, and interest has increased in the development of

components from natural sources with fewer adverse effects for preventing and ameliorating obesity. A lot of natural plants (e.g., herbs, fruits, and vegetables), functional fatty acids (e.g., polyunsaturated fatty acids and conjugated fatty acids), and different herbal dietary compounds were utilized in distinctive anti-obesity products. The presence of an abundant number of phytochemicals, fibers, and unsaturated fatty acids contributes to the biological benefits of these natural materials. Natural plant products are anticipated to be potential components for the development of nature-sourced anti-obesity products in the weight loss segment due to growing consumer health alertness. Natural supplement products primarily helping consumers to fight the battle against obesity have been widely explored. Shiikuwasa (Citrus depressa), Blueberry (Vaccinium ashei), Mulberry (Morus australis), Anthocyanins, Soybean (Glycine max), Coffee (Coffea Arabica), Lotus leaf with taurine (Nelumbo nucifera), Gingerol, paradol, and shogaol, Chili pepper (Capsicum annum), Turmeric (Curcuma longa), White mulberry (Morus alba) are some natural resources found to have anti-obesity effects.

Traditional Chinese medicine (TCM), for weight reduction, and its associated symptoms possessing a therapy modality with possible high efficacy and few harmful effects. Many TCM interventions have prolonged been used for the redress of ailments such as Type 2 diabetes, hypertension, and obesity. During the preceding decade, an awful lot of recent progress has been made in the find out about weight loss therapy with TCM. Researches, Clinical Trials, and Clinical investigations of TCM stated an appropriate number of TCM compounds are remarkable in the therapy, with possible mechanism and acceptable adverse reactions for therapy of obesity. As said, in every seed of good there is always a piece of bad, there is some imperfection in TCM too. CHM is composed of a variety of herbs and is prescribed primarily based on the unique Chinese medication theory—syndrome differentiation. The reproducibility of these trial designs besides Chinese medicine practitioners is therefore challenging. The drug composition of herbal medicine is complex, making it tough to determine the mechanism(s) of action, in contrast to in western medicine. Only a small range of the research covered in TCM has mentioned that the use of herbal medicinal drug preparations brought about adverse reactions. The safety of long-term use of herbal medicine wishes to be also explored. While most of the trial suggested no potential adverse effects amongst the TCM groups, some papers do report reasonable adverse outcomes associated with TCM use. Such as, a case of sudden death due to the use of green tea; A 19-year-old obese man (120 kg) who drank large amounts of green tea (15 cups per day) with a strict food regimen, over two months; lost 30 kg of body weight. However, after his common exercise, he died of left ventricular fibrillation. Therefore, the use of traditional Chinese medicines ought to be regulated. The safety of long-term use of herbal medication needs to be also analyzed.

The known ancient Chinese proverb "a bitter drug cures the unwellness," the bitter drugs relating to genus Coptis Chinensis, exemplifies its long history of use and recognition in people. Later, it's that the key active ingredient in the genus Coptis Chinensis is berberine. Medicinally, berberine has usage of history of about 3000 years in Ayurvedic, Iranian, and Chinese medicine. A quite large number of scientific research show that berberine can show its therapeutic activities in the remedy of distinctive diseases along with diabetes, hyperlipidemia, cancer, hypertension, stroke, metabolic syndrome, polycystic ovarian syndrome, and liver ailment in human subjects. Some researchers have also made insight into the anti-aging function of berberine too, due to its antioxidant properties.

Those findings have been no longer sufficient to sort out the poor bioavailability, less solubility, and cytotoxic aspect results of berberine for its use in clinical practice in an international vicinity. There has been a dire need for modified berberine with advanced pharmacokinetics, improved pharmacodynamic properties, and confined possible toxicity consequences. Recently, attention has come to light that the fully reduced form of berberine, i.e., tetrahydroberberine, has significant enhanced pharmacodynamics, improved pharmacokinetics, and reduced adverse reaction activity that differs from the parent berberine. Past efficient researches of berberine on obesity and though its advantageous outcomes of scientific trials, berberine has not been approved for any of the clinical uses in the United States.

III. Conclusion

Obesity, hazardous to human health is a complex, chronic disorder caused by an interaction of contributing factors, including dietary, lifestyle, genetic, and environmental factors. The unexpectedly increasing occurrence of obesity made it a global concern. More than one billion people are expected to be obese by 2030 globally. Present therapeutics of obesity in western medicine (WM) are confined due to poor tolerability and low compliance owing to associated side effects restricting their potential widespread use. Therefore, the development of additional drugs from traditional Chinese medicines (TCM) is currently arousing considerable interest due to the fact, the most in all likelihood have fewer side effects. Extensive preclinical and clinical researches have shown that the TCM compound, Berberine appears to be effective in weight reduction smoothly. However, poor intestinal absorption (< 5%) and rapid metabolism in the body, made it a drug with low oral bioavailability. The reduced form of berberine i.e tetrahydroberberine, tetrahydroberrubine with better pharmacology, greater acceptability, higher solubility, less toxicity and has expanded bioavailability than berberine.

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