
HERBAL MEDICAL PRODUCT FOR METABOLIC DISEASES: A NEW PHARMACOLOGICAL APPROACH

¹Uddappanda Bopaiah Roy, ²Seethalaxmi Radhakrishna, ³Renuka Jyothi S., ⁴Myrene Roselyn Dsouza, ⁵Parinitha Mahishi, ⁶Premalatha S.J. and ⁷*Sharangouda J. Patil

¹Department of Zoology and Genetics, Nrupathunga University, Bengaluru-560001 Karnataka, India

²Department of Biotechnology, Surana College, Bengaluru-560011, Karnataka, India

³Department of Life Science, School of Sciences, Jain University, Bengaluru-560002, Karnataka, India

⁴Department of Chemistry, Mount Carmel College, Bengaluru-560052, Karnataka, India

⁵Department of Botany, NMKRV College for Women, Bengaluru-560011, Karnataka, India

⁶Department of Studies in Biochemistry, Government Science College, Chitradurga - 577501, Karnataka, India

⁷*Department of Zoology, NMKRV College for Women, Bengaluru-560011, Karnataka, India

***Corresponding author:**

Sharangouda J. Patil, E-Mail: shajapatil@gmail.com

ABSTRACT

Herbal medications are widely used. They are frequently used in the underdeveloped countries, where they often provide pharmaceutical drugs with a more accessible and accessible alternative. As the use of herbal treatments became more widespread, people began to worry about the professionalism of practitioners as well as the quality, effectiveness, and safety of various treatment regimens as well as the available herbal and natural product options. Historically, concerns about public health have taken a back seat to concerns about regulatory hurdles and the safety, efficacy, and mechanism of action of clinical and experimental medicine. To optimize the contribution of herbal medicine to global health care systems, public health studies must take into account social, cultural, political, and economic circumstances. Currently being reviewed is the regulatory framework for dietary supplements and herbal medications. The marketing of products that adhere to quality and safety criteria will be made possible through a new registration system for traditional herbal remedies. Currently, there is cause for worry over the pharmaceutical quality of many supplemental medicines. WHO created criteria for the evaluation of herbal medicine in 1991. The standardization of natural medicines is suggested. We talk about the situation and how people view herbal medicine. Only by establishing regulatory criteria on these items, which should be produced adopting these Good Practices, would it be possible to determine whether the general public believes that natural and herbal remedies are safer than artificial ones. This article offers a comprehensive introduction to herbal medicine, covering its origins, uses, benefits, risks, quality assurance, clinical trials, drug interactions, bioavailability, marketing, regulations, and more.

Keywords: Herbal medical product, metabolic diseases, Metabolic syndrome (MS), pharmacological approach, Medicine.

INTRODUCTION

Metabolic diseases like type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD), and cancer are some of the most common health problems in the world. Changes in metabolism and energy homeostasis caused by these illnesses can lead to chronic diseases. Herbal extracts and other separate chemicals have been used to treat a wide range of diseases for hundreds of years, and they are now being looked at again as possible treatments for metabolic diseases. To treat these conditions, pharmacological methods must be used to make these kinds of medicines. Using computer methods, you can figure out how pharmacologically active an extract or metabolite is and come up with early ideas about likely targets and processes. Understanding the molecular processes that cause metabolic disorders and the possible benefits of herbal drugs, including herbal medical goods, could give us important

information about new therapeutic targets and ways to treat them [1, 2].

Herbal remedies have been used for centuries to treat a wide range of illnesses, and they also show promise in the management of metabolic diseases. To identify and assess the potential of herbal medicines as treatments for various disorders, pharmacological techniques are crucial [3-5].

Lifestyle disorders are characterized as alterations in a population's metabolism profile that are directly correlated with their daily routines [6, 7]. Unorganized eating patterns, unattended exercise routines, and other lifestyle factors are the main causes of lifestyle diseases. Metabolic syndrome is on the rise as a result of the obesity epidemic. Metabolic syndrome is a pathological condition characterized by abdominal obesity, insulin

resistance, hypertension, and hyperlipidemia, as defined by the World Health Organization. Syndrome X is also known by other names, such as insulin resistance. Prothrombotic disorders, proinflammatory states, nonalcoholic fatty liver disease, and reproductive issues are all examples of co-occurring ailments [7]. Diabetes is a long-term metabolic illness that has a significant negative impact on patients' socioeconomic level. In certain affluent countries, the prevalence of diabetes has gradually increased over the past few decades. If effective treatment measures are not put in place, the number of people with diabetes might rise by 693 million by the year 2045, according to estimates from the International Diabetes Federation (IDF) [8, 9].

The prevalence of diabetes has risen considerably over the past few decades, and this trend is expected to continue. 80 % of all deaths caused by NCDs (preventable diseases) are directly attributable to these particular concerns, along with malignancies, respiratory problems, and cardiovascular consequences [10, 11].

According to IDF data, diabetes is becoming a bigger problem in India. Between the ages of 20 and 70, there are an estimated 8.7% of people with diabetes [12]. Type 2 diabetes is a metabolic disorder associated with the metabolism of carbohydrates, fats, and proteins. It is followed by insulin resistance or deficiency. Thirst, polyuria, blurred vision, and weight loss are some of the telltale signs and symptoms of diabetes mellitus [13]. For more than 80 years, there has been a metabolic syndrome. Globally, the prevalence of metabolic syndrome has increased significantly during the past 20 years. This increase is related to the global epidemic of diabetes and obesity. The increased risk of diabetes and cardiovascular disease caused by the metabolic syndrome necessitates the creation of solutions to halt the looming global epidemic. [14].

A quarter to a third of persons from different ethnic backgrounds satisfy the criteria for the metabolic syndrome, according to studies from the last ten years. As people age, metabolic syndrome becomes more prevalent [15]. According to studies, Type 2 diabetes mellitus (T2DM) is more common in some racial and ethnic groups than others; for example, 15.0% of American Indians and 4.30% of Chinese Americans suffer from the disease. Compared to other ethnic groups, South Asian Americans are more likely to have metabolic syndrome and abdominal obesity [16]. Consistent smoking in the household, being overweight, living in poverty, being of Mexican descent, and being past menopause are all risk factors, sedentary lifestyle, heavy alcohol consumption, Western diet, lack of cardiorespiratory fitness, excessive television viewing,

and antiretroviral drug use all increase the likelihood of developing a metabolic disorder. Potential contributors to the pathophysiology of the metabolic components of the metabolic syndrome include insulin resistance and hyperinsulinemia [18]. Diabetes, atherosclerosis, prothrombotic, and inflammation are all made more likely by the metabolic syndrome, also known as hypoadiponectinemia [19]. One of the hallmarks of metabolic syndrome is an abnormality in the way fat is distributed throughout the body, particularly an accumulation of visceral fat. High plasma triglycerides, low HDL-C levels, and an excess of tiny, dense low-density lipoprotein (LDL) particles make up the "lipid triad" that is a hallmark of the dyslipidemia of the metabolic syndrome and a leading risk factor for atherosclerotic cardiovascular disease. Modifying one's way of life to promote healing is an integral aspect of care. Using medication may be necessary if dyslipidemia is not treated. Statins are the first line of treatment for lowering LDL-C [20]. Visceral fat reduction along with a change in lifestyle may be an effective treatment for metabolic syndrome patients who want to avoid atherosclerotic cardiovascular disease (ACVD) [21].

MANAGEMENT OF METABOLIC SYNDROME WITH HERBAL MEDICINE

Millions of people throughout the world suffer from the metabolic condition known as diabetes mellitus (DM). Diabetes is brought on either insufficient insulin production or insufficient pancreatic insulin synthesis. Despite the fact that several synthetic drugs have been created, none of them offer a full recovery. Despite the fact that prolonged usage of some synthetic substances might have serious side effects, there is still a demand for affordable, nontoxic medicines. Traditional medical practices have been revered throughout the course of human history. These are widely used throughout the world, proving the growing significance of herbs in contemporary, cutting-edge medicine. Out of the 21,000 plants that are utilized for therapeutic purposes globally, the World Health Organization (WHO) estimates that 400 plants can be used to treat diabetes [22, 23].

Numerous herbs, including those in pharmaceutical forms made with nanotechnology and containing Metabolic syndrome may be treated with plant extracts or bioactive components. Researchers and doctors are looking into new, secure, complementary, and alternative therapy options for this widespread issue. It has been discovered that using herbal medicines can help people shed weight and body fat. Various preclinical and clinical studies have looked at the benefits of herbal medications include treatment of diabetes and obesity and reduction of inflammation and free radical damage [24]. The benefits of using medicinal plants as a straightforward,

affordable, and natural alternative treatment for metabolic disorders in the healthcare system. Herbal medications decrease gluconeogenesis, inflammation, and oxidative stress while increasing insulin secretion and cardiovascular health. Many plant extracts have been suggested as possible treatments for diabetes and related effects. By controlling their pharmacokinetics and increasing their body availability, nano structured formulations of herbal extracts might enhance their anti-diabetic actions [25].

Despite the potential for major adverse effects from continuous use of some synthetic compounds, there is still a demand for accessible, nontoxic medications. Traditional treatments have a long history of being thought of as being very successful. These are frequently utilized all throughout the world, demonstrating the growing importance of herbs in cutting-edge, contemporary medicine. Low side effects are one of the key advantages of herbal medicines, It has prompted a plethora of scientists to work on cutting-edge compounds for diabetic treatment. Numerous herbal substances are currently undergoing various phases of clinical investigation for their potential to treat diabetes and avoid its effects [26].

Numerous herbal treatments, like the capsicum family's capsicum annum, showed anti-diabetic effects in clinical studies by enhancing peripheral insulin sensitivity, reducing insulin levels, and improving glucose tolerance. Capsaicin, the main ingredient in capsicums, stimulates the release of GLP-1, increasing glucagon levels in the blood and decreasing levels of ghrelin (an orexigenic hormone). The activities of α -amylase and α -glucosidase are suppressed, according to preclinical research [27].

Saffron, the dried stigma of the *Crocus sativus* plant, is used as a spice and a natural dye. It has been shown to have an anti-hyperglycemic effect by lowering serum blood glucose levels and an antioxidant effect in rats with diabetes induced by streptozotocin. In addition to dephosphorylating Akt, it also dephosphorylates AMP-activated protein kinase and mitogen-activated protein kinase [28].

The most effective plant extracts for lowering fasting blood sugar (FBS) have been found to be green tea (at 150 and 1000 mg/day), hibiscus sabdariffa (at 1000 mg/day), tea (10 g/day), cinnamon (at 550 and 3000 mg/day), and many more. Use of *Hibiscus sabdariffa*, *Citrus aurantium*, *Sea buckthorn*, *Bilberries*, *Proteus vulgaris*, and *Ceratonia siliqua*, as well as a combination of grape seeds and pine wood, was also associated with a significant decrease in HbA1C. *Rhus coriaria* L. and

chia, a plant, have also been shown to increase insulin secretion in two separate investigations [29].

Fasting blood glucose, triglyceride, low-density lipoprotein, and hemoglobin A1c were all reduced after several months of treatment with aloe vera extract capsules (300 mg/kg). Aloe vera powder (100, 200 mg/kg) was given orally over the course of three months to lower fasting and postprandial glucose levels, as well as blood pressure [30].

Other herbal remedies or extracts, primarily used in Asia, reduced levels of both fasting and post-meal glucose via interacting with the GLUT-4 receptor. When used in conjunction with anti-diabetic medication, fenugreek boosted insulin sensitivity and reduced blood sugar levels. Chinese extract Yuquan Wan, which was given for a month, reduced FBS and alleviated problems caused by diabetes. Chinese herb Xioake Wan (XAX), Significant improvements in blood lipid and blood glucose indices were observed when anti-diabetic medicines were combined with enhanced insulin sensitivity. Most people don't get their hypertension under control or treat it. The efficient management of hypertension is hampered by the accessibility, expense, and adverse effects of antihypertensive medications [31].

Several symptoms of hypertension were not relieved by conventional treatment. Dietary and lifestyle changes, as well as combination therapies with herbs, are among the most often used alternative treatments for hypertension. In general, herbal medicines have positive side effects without causing any harm. Nearly all health stores sell herbal treatments, which can be obtained without a prescription. You can grow some herbs in your backyard. For those who have a range of pharmaceutical allergies, these treatments are ideal. The most common illness in the world is hypertension. Because their hypertension is asymptomatic, patients who are given pharmaceutical therapy may decline it and choose alternative treatments [32].

In animal studies, *Panax ginseng* (3 g/kg) was used for 12 weeks to reduce arterial stiffness and systolic blood pressure via activating endothelial nitric oxide synthase (eNOS) and the nitric oxide pathway. Many of the synthetic medications on the market now come with serious health risks. Herbal supplements can be used in place of or in addition to pharmaceutical treatment for weight loss and maintenance. They are more advantageous, safer, and cheaper than conventional pharmaceuticals. Treatment of metabolic disorders using pharmacodynamic bioactive compounds found in medicinal plants is both synergistic and additive. There are multiple processes through which herbs can aid in

weight loss and maintenance. These include suppressing appetite and increasing fullness, increasing energy expenditure, facilitating low-fat digestion, and accelerating fat lipolysis [33].

Obesity is a metabolic disorder marked by an abnormal buildup of body fat. It is associated with an increased risk of conditions such as diabetes mellitus type 2, hypertension, dyslipidemia, osteoarthritis, renal illness, insomnia, etc. Despite continued research funding, there are currently only a few efficient medications for treating obesity. The use of medicinal plants and their byproducts is one supplemental and alternative treatment option that patients and researchers are looking for as a result of obesity. Research suggests that herbal plants may be an alternate treatment for hyperlipidemia in patients who are unable to tolerate statins or who refuse to take current antihyperlipidemic medications [34].

Capsaicin (6 mg/kg) was used for 12 weeks in a clinical experiment, and it was shown that there was a considerable fat decrease. An active component of capsicum plants and a water-soluble homovanillic acid derivative known as capsaicin, has a number of anti-inflammatory effects on a variety of conditions, including anorexia, hemorrhoids, migraines, and skin conditions. Recent in vivo and in vitro studies show that it acts as an antihyperlipidemic medication by activating peroxisome proliferator activated receptor (PPAR-), reducing intestinal absorption, and enhancing bile acid synthesis.

In turn, activation of peroxisome proliferator-activated receptors (PPARs) reduces low-density lipoprotein (LDL), triglycerides, and serum cholesterol while elevating high-density lipoprotein (HDL) levels. [35].

RELATIONSHIP BETWEEN AYURVEDA AND MODERN MEDICINE

The development of pharmaceutical therapies for chronic disorders has benefited greatly from the insights provided by Ayurveda, a well-known ancient medical system in India. Combining the vast knowledge base of ancient systems like ayurveda with the impressive powers of combinatorial sciences and High Throughput Screening could be beneficial for the development of structure-activity libraries. Utilizing Ayurvedic knowledge and experiential databases may be able to provide brand-new functional leads for overcoming the main difficulties associated with medication development, including time restraints, financial burdens, and toxicity-related problems. The extensive historical use of these drugs, which have undergone thorough research on human beings over many centuries, gives the aforementioned records substantial value. An extensive corpus of pharmacoepidemiological evidence regarding the use and safety of ayurvedic medicines is still being worked on. The New Millennium Indian Technology Leadership Initiative (NMITLI) at the Council for Scientific and Industrial Research (CSIR) is developing standardized herbal formulations [36].

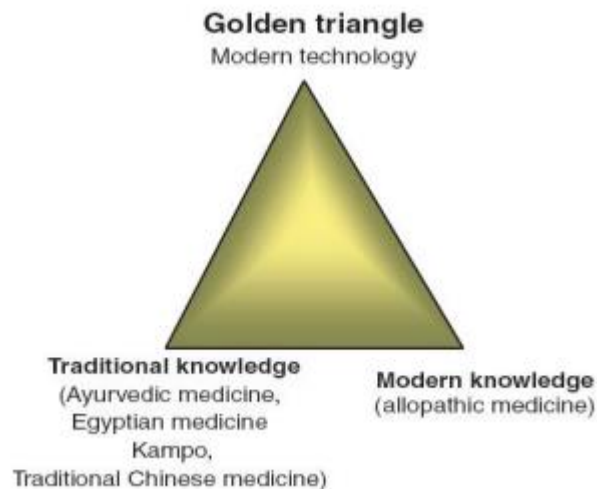


Figure 1: Relationship between Ayurveda and modern medicine.

NATURAL REMEDIES FOR DIABETES CONTROL

In addition to a lengthy history of using natural items as medicine, alternative therapies are becoming incredibly popular and widely used. According to a telephone poll

conducted in the US in 2002, 18.8% of adult Americans use herbal or other natural products as dietary supplements on a weekly basis. Alternative medications for the treatment of diabetes should be taken into consideration because synthetic anti-diabetic medications

might have negative effects, such as severe hypoglycemia, and they may not be safe in some situations. Alternative medicines should often be more affordable, safer, and accessible. WHO estimates that between 65% and 80% of the global population resides in low- and middle-income countries. This group need access to natural treatments due to a shortage of modern medical resources. Alternative treatment also seems to be more in line with the beliefs and values of patients. Herbal therapy is one of the most popular alternative treatments, and it plays an important part in the management of diabetes in both Eastern and certain Western countries like Germany, France, Italy, and the United States. Although modern medicine has made rapid advancements in recent years, plants continue to be an important part of healthcare and prescription drugs [37].

Natural goods are still a promising source for the development of new drugs, as seen by the high number of molecules derived from natural products that are currently undergoing clinical studies. Although there is some evidence for the safety and effectiveness of herbal treatments, it is not enough, and further systematic reviews and meta-analyses are required [38].

Polyphenols

Most phenolic compounds in plants are aromatic compounds. Anthocyanins and flavonoids make up this class. There are five types of flavonoids: flavonols, flavanols, flavones, and isoflavones. The ability of plants of this genus to chelate metals, activate antioxidant enzymes, and scavenge free radicals has earned them widespread recognition. They can boost cellular resilience to oxidative stress and reduce the negative effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Recently, a thorough evaluation of randomized controlled clinical studies using resveratrol as an additional T2DM treatment was conducted. For systolic blood pressure, HbA1C, and creatinine, the results showed that resveratrol had statistically significant advantages over placebo/control, but not for fasting glucose, the HOMA index, diastolic blood pressure, insulin, or lipid profiles.

The three main isoflavones found in the human diet genistein, daidzein, and glycitein come primarily from soy. Genistein is the most common isoflavone found in soybeans. Genistein can boost pancreatic insulin secretion as well as peripheral glucose absorption [40].

Turmeric is mostly composed of the polyphenol curcumin as diferuloylmethane, which is used as a culinary spice. The *Curcuma longa* plant, from which it is extracted, has been used for centuries in Ayurvedic and

Ayurvedic medicine in China and India. Scavenging free radicals, reducing adhesion molecules and antiapoptotic proteins, blocking pro-inflammatory cytokines, and blocking lipid peroxidation are just some of its antioxidative activities [41].

Nrf2 activators

To address conditions brought on by oxidative stress, numerous Nrf2 activators have been discovered. The synthetic triterpenoid bardoxolone methyl and the natural isothiocyanate sulforaphane, found in broccoli sprouts, are two such activators now employed in clinical investigations. However, preliminary findings from a bardoxolone methyl phase 3 clinical trial in people with type 2 diabetes and chronic renal disease suggested that researchers need to be more cautious when modifying this pathway [42].

Herbal phosphodiesterase inhibitors

The PDEIs can inhibit phosphodiesterase while increasing cAMP and cGMP. A study found a correlation between PDEIs' anti-inflammatory and antioxidant effects and a decline in reduced levels of lipid peroxidation and oxidative stress, increased antioxidant ability, and enhanced performance of cultured islet cells [43].

Octanoic acid is the precursor to a dithiol molecule termed -lipoic acid. Antioxidant recycling, chelation of metal ions, and free radical scavenging are only a few of its antioxidative properties. Retinopathy, neuropathy, and impaired nerve transmission and blood flow have all been successfully simulated in animal models of diabetes [44].

Pineal gland-produced melatonin (5-methoxy-n-acetyltryptamine) can minimize oxidative stress and slow the development of tumors. It prevents DNA, protein, and membrane damage by acting as an antioxidant. The activity of catalase (CAT) is enhanced, but hepatic glutathione peroxidase (GSH-Px) activity is decreased, and lipid peroxidation is reduced [45].

ANTI-OBESITY EFFECTS OF NATURAL TREATMENTS

Herbal treatments for obesity have been shown to be effective in clinical trials, with benefits including decreased body weight, fat mass, waist and hip circumferences, and food intake, as well as anti-hyperglycemic, anti-hyperlipidemic, and anti-oxidative effects. The following plants have been shown to have anti-obesity effects [46]. These characteristics include a decrease in the rate of lipid absorption and energy intake and an increase in the rate of energy expenditure, as well

as a decrease in the rate of pre-adipocyte differentiation and proliferation, lipogenesis, and lipolysis.

Ephedra and caffeine supplements, *Caralluma fimbriata*, hydroxycitric acid, fenugreek fiber, epigallocatechin from green tea, and a naturally occurring complex comprising capsicum and numerous lipotropic components all have an effect on food intake. In addition to lowering blood cholesterol levels and suppressing hunger, *Agave tequilana*, *Dasyliion* spp., Pomegranate leaf, Korean red ginseng, Tree peony root, and Gyeong Shang angjeehwan may also change hormonal balance [47].

Polyphenols, terpenoids, organosulfur, and phytosterols are the four basic types of dietary phytochemicals. They are effective anti-obesity medicines because they restrict the formation of adipose tissue, stop the differentiation of pre-adipocytes, activate lipolysis, and induce apoptosis to decrease adipose tissue mass [48].

Polyphenols

One member of the stilbenes subclass of polyphenols is resveratrol. Antioxidant and anti-obesity properties of resveratrol are present. More so than its modest ROS-scavenging activity, its impact on redox enzymes is largely responsible for its protective action against oxidative stress. Resveratrol can boost eNOS expression and activity, promote antioxidant enzymes, and inhibit eNOS uncoupling. Its effects on fat mass, the activity of calorie-restrictive enzymes, lipolysis, and activation of apoptosis are all anti-obesity. It also reduces adipogenesis and viability in maturing preadipocytes. Additionally, it decreases lipid synthesis and proliferation, blocks TNF-activated NF- κ B signaling, modifies the expression of adipokines, and raises insulin sensitivity.

Curcumin is yet another instance of a polyphenol from the curcuminoid subclass. In addition to decreasing curcumin protects the liver from damage, inhibits LDL-C oxidation, boosts adiponectin production, reduces body weight gain, and controls the expression of genes involved in energy metabolism, lipid accumulation, and lipogenesis, such as PPAR. Additionally, it can reduce angiogenesis, inflammation linked to obesity, and metabolic conditions like insulin resistance, hyperglycemia, and hyperlipidemia brought on by obesity.

Terpenoids

The terpenoids make up a sizable portion of the natural product family tree. Lycopene is a type of terpene that belongs to the carotenoid family. Lycopene is an effective antioxidant that prevents lipid and LDL-C

oxidation. In addition to regulating the immune system and hormones, it also inhibits cell proliferation, reduces pro-inflammatory markers, induces apoptosis in target cells, and inhibits the generation of pro-inflammatory indicators by tumor necrosis factor (TNF) [51].

Organosulfur

Allium species, such as garlic and onion, have a very high concentration of organosulfur compounds, which are rich in bioactive chemicals including allicin, allixin, and allylsulfides. Reducing the activity of inflammatory enzymes, decreasing the expression of iNOS in macrophages, decreasing the production of inflammatory signaling molecules, decreasing the number of fat cells, and having overall antioxidative effects are all the result of inhibiting hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase [52].

Seeds, nuts, and vegetable oils are the primary food sources of phytosterols. They protect against atherosclerosis by decreasing total and LDL-C levels in the blood and blocking the absorption of cholesterol in the intestines. This community relies on *Commiphora mukul*, a plant that has been promoted as a weight-loss aid. The chemical element guggulsterone is responsible for the beneficial effects on cholesterol, blood sugar, HDL cholesterol, and inflammation. In addition, guggulsterone can increase PPAR expression and activity while decreasing adipocyte differentiation [53].

Omega-3 fatty acids

Oral omega-3 supplementation's effects on body weight and body composition have been studied in a number of clinical trials. Several research have claimed that it has a positive impact on fat mass and waist circumference, despite inconsistent conclusions from the available information.

NATURAL REMEDIES FOR MANAGEMENT OF OSTEOPOROSIS

There is a growing need for complementary and alternative medicine in the care of osteoporosis due to reports of harmful effects of pharmacotherapy (estrogens, bisphosphonates). Epidemiological studies and therapeutic treatments have both confirmed the positive effects of antioxidants on bone health and osteoporosis. Numerous recent studies on medicinal herbs have demonstrated the antioxidant effects they can have on osteoporosis. Omega-3 fatty acids and phytoestrogens are two further examples of naturally occurring chemicals. Herbal supplements that are said to be good for your bones include soy isoflavones, black cohosh, *Fructus linguistri lucidi*, and *Cissus quadrangularis*, all of which have been the subject of clinical trials [54].

Lycopene

The antioxidant carotenoid lycopene has a capacity to quench singlet oxygen that is ten times more than that of -tocopherol and two times that of β -carotene. Tomatoes, watermelons, pink guavas, and pink grapefruit are some of its main food sources. Lycopene is absorbed best when tiny amounts of lipids are present since it is fat-soluble. Most of lycopene's health advantages may come from its powerful antioxidant qualities. Lycopene promotes osteoblast cell growth and alkaline phosphatase activity. Bone mineral density (BMD) is improved, the proliferation of ROS-releasing osteoclasts is inhibited, and the risk of osteoporosis-related fragility fracture is decreased [55].

Polyphenols

Polyphenols, a type of antioxidant, are naturally found in plants. People like drinking tea, which is created from the *Camellia sinensis* leaves are dried and sent over the world. Polyphenols in tea have been shown to enhance bone density, prevent bone loss, and counteract inflammation. EGCG, which is abundant in green tea, is the polyphenol that has received the most attention. Matrix metalloproteinase 9 (MMP-9) expression and growth are both suppressed by EGCG, which also inhibits thyroid hormone-stimulated osteocalcin synthesis in osteoblasts and rat osteoclast formation and differentiation. Furthermore, EGCG induces human osteoblast-like cells to form more mineralized bone nodules. Multiple biological signals, including MAPK, BMP, and OPG/RANKL, can be modulated by polyphenols to influence osteoblast function. There are more polyphenols with positive effects. The negative effects of tumor necrosis factor (TNF)- on osteoblast function can be mitigated, for instance, by consuming dried plum. Oleuropein can be used to control how bone marrow stem cells develop.

Omega-3 fatty acids

Fish, eggs, walnuts, and flax seed all contain omega-3 fatty acids in varying amounts. They help the intestines better absorb calcium in addition to acting as antioxidants. Omega-3 has been shown to increase bone turnover and decrease bone resorption, improving bone mineral density (BMD) in the hip, lumbar spine, and entire body. They can also change interleukin-1, interleukin-6, and TNF- production, as well as prostaglandin synthesis [57].

Phytoestrogens

Phytoestrogens include substances including isoflavones, lignans, flavonoids, stilbenes (resveratrol), and coumestans. They are believed to act as potent antioxidants, bind to estrogen receptors, and inhibit cytochrome P450 and aromatase. The risk of prostate,

breast, and adrenal cancer can increase if there is a high quantity of the enzyme aromatase, which converts androgens into estrogens. A significant increase in bone strength, a reduction in fracture risk, an improvement in lumbar spine bone mineral density (BMD), and a significant decrease in urine deoxypyridinoline, a marker of bone resorption, were observed in postmenopausal women who consumed soy isoflavones, while serum alkaline phosphatase and osteocalcin, markers of bone formation, were unaffected.

Even though isoflavones have been the subject of numerous clinical investigations, there are still many unanswered issues about which metabolite and at what dose might provide the most health advantages. However, non-hormonal therapy for menopausal symptoms will always be needed. Phytoestrogen therapy may be the best option because it does not cause tumors to grow in response to estrogen [59].

CONCLUSION

Patients with lifestyle issues run the risk of contracting thromboembolic illness, atrial fibrillation, stroke, aortic stenosis, and heart disease. The findings suggests that the risk of ischemic stroke in those with metabolic syndrome may now be significantly higher than previously believed. Having an increased likelihood of developing colon, kidney, and gallbladder malignancies is one of the additional problems connected to metabolic syndrome. Additionally, cognitive dysfunction may be more likely as a result of metabolic syndrome. Finally, individuals with metabolic syndrome are more likely to be classified as polypharmacy, which entails higher medical costs, a higher likelihood of poverty, and more challenging access to high-quality care. Crude medications are secure and are anticipated to improve metabolic syndrome. Complementary and alternative medical treatments will become efficient treatments. Because they are trustworthy, non-toxic, and cost-effective in this situation to avoid the negative side effects and financial burdens associated with pharmaceuticals, patients trust alternative treatments like plant-based medicines.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors approved the manuscript for publication.

Availability of data and material

All required data is available.

Competing interests

All authors declare no competing interests.

Funding

Not applicable.

REFERENCES

1. Tabatabaei-Malazy, O., Larijani, B. and Abdollahi, M., 2015. Targeting metabolic disorders by natural products. *Journal of Diabetes & Metabolic Disorders*, 14, pp.1-21.
2. Surana, K.R., Ahire, E.D., Sonawane, V.N., Talele, S.G. and Talele, G.S., 2021. Molecular modeling: Novel techniques in food and nutrition development. *Natural Food Products and Waste Recovery*, pp.17-31.
3. Li, F.S. and Weng, J.K., 2017. Demystifying traditional herbal medicine with modern approach. *Nature plants*, 3(8), pp.1-7.
4. Singh, A., Diwaker, M., Thakur, A., Surana, K., Chopra, M., Kumar, H. and Sharma, S., 2023. Regioselective Pd-catalyzed decarboxylative C-6 acylation of 7-O-carbamate coumarins and their anti-inflammatory evaluation. *Tetrahedron*, 134, p.133295.
5. Suryawanshi, Hemant P., Rane, Bhushan R. and Keservani, Raj K. (2023) Beneficial Effect of Dietary Fibers in metabolic Induced Obesity, In: *The Metabolic Syndrome: Dietary Supplements and Food Ingredients*, Edited by Keservani, Raj K., Yadav, Durgavati., Keservani, Rajesh K., Singh, Sippy., Sandeep, Kumar. Apple Academic Press, CRC Press, Taylor & Francis Group, chap 12, pp. 251-2709. ISBN: 978-1-77491-111-2.
6. Chawla, R., Thakur, P., Chowdhry, A., Jaiswal, S., Sharma, A., Goel, R., Sharma, J., Priyadarshi, S.S., Kumar, V., Sharma, R.K. and Arora, R., 2013. Evidence based herbal drug standardization approach in coping with challenges of holistic management of diabetes: a dreadful lifestyle disorder of 21st century. *Journal of Diabetes & Metabolic Disorders*, 12, pp.1-16.
7. Jarouliya, U., Keservani, Raj K. (2019). "Pathways Leading to Child Obesity", *Global Perspectives on Childhood Obesity: Current Status, Consequences and Prevention*, Second Edition, Edited by Debasis Bagchi, Academic Press, Elsevier, chapter 12, pages 137-146. ISBN: 9780128128404.
8. Zhang, A., Sun, H. and Wang, X., 2018. Mass spectrometry-driven drug discovery for development of herbal medicine. *Mass spectrometry reviews*, 37(3), pp.307-320.
9. Nanjappan, S., Paul, D. and Bolla, L., 2018. Assessing herb–drug interactions of herbal products with therapeutic agents for metabolic diseases: analytical and regulatory perspectives. *Studies in natural products chemistry*, 59, pp.283-322.
10. Sharma, Anil K., Keservani, Raj K., Gautam Surya P. (2020). *Herbal Product Development*, Apple Academic Press, CRC Press, Taylor & Francis Group. Pp. 1-376. ISBN: 9781771888776.
11. Rane, Bhushan R., Bharath, Mounika S., Patil, Rutuja R., Keservani, Raj K., Jain, Ashish S. (2020b). Novel Approaches in Nutraceuticals, In: *Enhancing the Therapeutic Efficacy of Herbal Formulations through Novel Drug Delivery Systems* Edited by Rajesh Kumar Kesharwani, Raj K. Keservani, Anil K. Sharma, IGI Global International Publisher, Pennsylvania, USA, Chapter 11, 241-266. ISBN13: 9781799844532.
12. Keservani, R.K., Kesharwani, R.K., Sharma, A.K., Gautam, S.P. and Verma, S.K., 2017. Nutraceutical formulations and challenges. In *Developing new functional food and nutraceutical products* (pp. 161-177). Academic Press.
13. Rane, Bhushan R., Patil, Aishwarya S., Keservani, Raj K., Jain, Ashish S. (2020a). Novel Approaches in Herbal Formulation, In: *Enhancing the Therapeutic Efficacy of Herbal Formulations through Novel Drug Delivery Systems* Edited by Rajesh Kumar Kesharwani, Raj K. Keservani, Anil K. Sharma, IGI Global International Publisher, Pennsylvania, USA, Chapter 2, 43-68. ISBN13: 9781799844532.
14. Lu, Z., Zhong, Y., Liu, W., Xiang, L. and Deng, Y., 2019. The efficacy and mechanism of Chinese herbal medicine on diabetic kidney disease. *Journal of diabetes research*, 2019.
15. Parasuraman, S., 2018. Herbal drug discovery: challenges and perspectives. *Current Pharmacogenomics and Personalized Medicine (Formerly Current Pharmacogenomics)*, 16(1), pp.63-68.
16. Cao, Y.J., Li, H.Z., Sun, Y.M., Li, X.Q., Chen, L. and Jin, X.W., 2022. Integration of multi-omics in investigations on the mechanisms of action of Chinese herbal medicine interventions in metabolic diseases. *Tradit Med Res*, 7(4), p.31.
17. Yan, T., Yan, N., Wang, P., Xia, Y., Hao, H., Wang, G. and Gonzalez, F.J., 2020. Herbal drug discovery for the treatment of nonalcoholic fatty liver disease. *Acta Pharmaceutica Sinica B*, 10(1), pp.3-18.
18. Castro, M., Preto, M., Vasconcelos, V. and Urbatzka, R., 2016. Obesity: The metabolic disease, advances on drug discovery and natural product research. *Current topics in medicinal chemistry*, 16(23), pp.2577-2604.
19. Dutra, R.C., Campos, M.M., Santos, A.R. and Calixto, J.B., 2016. Medicinal plants in Brazil: Pharmacological studies, drug discovery, challenges and perspectives. *Pharmacological research*, 112, pp.4-29.
20. Fang, J., Little, P.J. and Xu, S., 2018. Atheroprotective effects and molecular targets of tanshinones derived from herbal medicine danshen. *Medicinal research reviews*, 38(1), pp.201-228.
21. Rane, Bhushan R., Tadavi, Sandip A., Keservani, Raj K. (2020c). "Naturopathy" In: *Herbal Product Development*, Edited By, Anil K. Sharma, Raj K. Keservani, Surya Prakash Gautam, Apple Academic Press, CRC Press, Taylor & Francis Group, Chapter 12, 321-347. ISBN: 9781771888776.
22. Andrade, C., Gomes, N.G., Duangsrissai, S., Andrade, P.B., Pereira, D.M. and Valentao, P., 2020. Medicinal

- plants utilized in Thai Traditional Medicine for diabetes treatment: ethnobotanical surveys, scientific evidence and phytochemicals. *Journal of ethnopharmacology*, 263, p.113177.
23. Panossian, A.G., Efferth, T., Shikov, A.N., Pozharitskaya, O.N., Kuchta, K., Mukherjee, P.K., Banerjee, S., Heinrich, M., Wu, W., Guo, D.A. and Wagner, H., 2021. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress-and aging-related diseases. *Medicinal research reviews*, 41(1), pp.630-703.
24. Yuan, S., Wang, Q., Li, J., Xue, J.C., Li, Y., Meng, H., Hou, X.T., Nan, J.X. and Zhang, Q.G., 2022. Inflammatory bowel disease: an overview of Chinese herbal medicine formula-based treatment. *Chinese Medicine*, 17(1), pp.1-17.
25. Pawar, S.D., Deore, S.D., Bairagi, N.P., Deshmukh, V.B., Lokhande, T.N. and Surana, K.R., 2023. Vitamins as Nutraceuticals for Anemia. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.253-279.
26. Tao, W., Xu, X., Wang, X., Li, B., Wang, Y., Li, Y. and Yang, L., 2013. Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal Radix Curcumae formula for application to cardiovascular disease. *Journal of ethnopharmacology*, 145(1), pp.1-10.
27. Rane, Bhushan R., Ahirrao, Rajesh A., Gujarathi, Nayan A., Jain Ashish S. and Keservani, Raj K. (2023) Pathophysiology and application of herbs in the metabolic Syndrome, In: *The Metabolic Syndrome: Dietary Supplements and Food Ingredients*, Edited by Keservani, Raj K., Yadav, Durgavati., Keservani, Rajesh K., Singh, Sippy., Sandeep, Kumar. Apple Academic Press, CRC Press, Taylor & Francis Group, chap 10, pp. 199-230. ISBN: 978-1-77491-111-2.
28. Ahire, E.D., Surana, K.R., Sonawane, V.N., Talele, S.G., Kshirsagar, S.J., Laddha, U.D., Thombre, N.A. and Talele, G.S., 2023. Immunomodulation Impact of Curcumin and Its Derivative as a Natural Ingredient. In *Nutraceuticals and Functional Foods in Immunomodulators* (pp. 253-269). Singapore: Springer Nature Singapore.
29. Patel, D.K., Kumar, R., Laloo, D. and Hemalatha, S., 2012. Diabetes mellitus: an overview on its pharmacological aspects and reported medicinal plants having antidiabetic activity. *Asian Pacific Journal of Tropical Biomedicine*, 2(5), pp.411-420.
30. Parkhe, A.G., Surana, K.R., Ahire, E.D., Mahajan, S.K., Patil, D.M. and Sonawane, D.D., 2023. Impact of Vitamins on Immunity. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.87-106.
31. Caliceti, C., Franco, P., Spinozzi, S., Roda, A. and FG Cicero, A., 2016. Berberine: new insights from pharmacological aspects to clinical evidences in the management of metabolic disorders. *Current Medicinal Chemistry*, 23(14), pp.1460-1476.
32. Ahire, E.D., Keservani, R.K., Surana, K.R., Singh, S. and Kesharwani, R.K. eds., 2023. *Vitamins as Nutraceuticals: Recent Advances and Applications*.
33. Tao, X., Yin, L., Xu, L. and Peng, J., 2018. Dioscin: A diverse acting natural compound with therapeutic potential in metabolic diseases, cancer, inflammation and infections. *Pharmacological Research*, 137, pp.259-269.
34. Gaikwad, J., Jogdand, S., Pathan, A., Mahajan, A., Darak, A., Ahire, E.D. and Surana, K.R., 2023. Nutraceuticals Potential of Fat-Soluble Vitamins. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.107-128.
35. Fimognari, C., Barrajon-Catalan, E., Luceri, C., Turrini, E., Raschi, E. and Bigagli, E., 2022. New regulation on medical devices made of substances: Opportunities and challenges for pharmacological and toxicological research. *Frontiers in Drug Safety and Regulation*, 2, p.1001614.
36. Adetuyi, B.O., Oline, G.O., Olajide, P.A., Adetuyi, O.A., Atanda, O.O. and Oloke, J.K., 2022. Nutraceuticals: role in metabolic disease, prevention and treatment. *World News of Natural Sciences*, 42, pp.1-27.
37. Guo, R., Luo, X., Liu, J., Liu, L., Wang, X. and Lu, H., 2020. Omics strategies decipher therapeutic discoveries of traditional Chinese medicine against different diseases at multiple layers molecular-level. *Pharmacological research*, 152, p.104627.
38. Mathur, S. and Hoskins, C., 2017. Drug development: Lessons from nature. *Biomedical reports*, 6(6), pp.612-614.
39. Khairnar, S.S., Surana, K.R., Ahire, E.D., Mahajan, S.K., Patil, D.M. and Sonawane, D.D., 2023. Structure and Functions of Vitamins. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.35-60.
40. Negi, H., Gupta, M., Walia, R., Khataibeh, M. and Sarwat, M., 2021. Medicinal plants and natural products: More effective and safer pharmacological treatment for the management of obesity. *Current Drug Metabolism*, 22(12), pp.918-930.
41. Yang, S., Li, D., Yu, Z., Li, Y. and Wu, M., 2021. Multi-pharmacology of berberine in atherosclerosis and metabolic diseases: potential contribution of gut microbiota. *Frontiers in Pharmacology*, 12, p.709629.
42. Sun, H., Zhang, A. and Wang, X., 2012. Potential role of metabolomic approaches for Chinese medicine syndromes and herbal medicine. *Phytotherapy Research*, 26(10), pp.1466-1471.
43. Wu, G., Zhang, W. and Li, H., 2019. Application of metabolomics for unveiling the therapeutic role of traditional Chinese medicine in metabolic diseases. *Journal of Ethnopharmacology*, 242, p.112057.
44. Singh, D.B., Pathak, R.K. and Rai, D., 2022. From traditional herbal medicine to rational drug discovery:

- strategies, challenges, and future perspectives. *Revista Brasileira de Farmacognosia*, 32(2), pp.147-159.
45. Zhao, X., An, X., Yang, C., Sun, W., Ji, H. and Lian, F., 2023. The crucial role and mechanism of insulin resistance in metabolic disease. *Frontiers in Endocrinology*, 14, p.1149239.
46. Taghipour, Y.D., Hajialyani, M., Naseri, R., Hesari, M., Mohammadi, P., Stefanucci, A., Mollica, A., Farzaei, M.H. and Abdollahi, M., 2019. Nanoformulations of natural products for management of metabolic syndrome. *International journal of nanomedicine*, pp.5303-5321.
47. Lokhande, T.N., Varma, K.S., Gharate, S.M., Mahajan, S.K. and Surana, K.R., 2023. Vitamins as Nutraceuticals for Pregnancy. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.185-204.
48. Wang, X., Zhang, A., Sun, H., Han, Y. and Yan, G., 2016. Discovery and development of innovative drug from traditional medicine by integrated chinmedomics strategies in the post-genomic era. *TrAC Trends in Analytical Chemistry*, 76, pp.86-94.
49. Wang, Y., Hu, B., Feng, S., Wang, J. and Zhang, F., 2020. Target recognition and network pharmacology for revealing anti-diabetes mechanisms of natural product. *Journal of Computational Science*, 45, p.101186.
50. Surana, K.R., Ahire, E.D., Patil, S.J., Mahajan, S.K., Patil, D.M. and Sonawane, D.D., 2023. Introduction to Nutraceutical Vitamins. *Vitamins as Nutraceuticals: Recent Advances and Applications*, pp.1-34.
51. Shende, P. and Narvenker, R., 2021. Herbal nanotherapy: A new paradigm over conventional obesity treatment. *Journal of Drug Delivery Science and Technology*, 61, p.102291.
52. Mosihuzzaman, M., 2012. Herbal medicine in healthcare-an overview. *Natural Product Communications*, 7(6), p.1934578X1200700628.
53. Surana, K., Chaudhary, B., Diwaker, M. and Sharma, S., 2018. Benzophenone: A ubiquitous scaffold in medicinal chemistry. *MedChemComm*, 9(11), pp.1803-1817.
54. Ahire, E.D., Surana, K.R., Sonawane, V.N., Talele, S.G., Talele, G.S., Kshirsagar, S.J., Khairnar, S.J. and Thombre, N.A., 2023. The Metabolic Syndrome: A Concerning Area for Future Research. In *The Metabolic Syndrome* (pp. 231-249). Apple Academic Press.
55. Surana, K., Ahire, E.D., Pawar, R., Khairnar, R., Mahajan, S., Kshirsagar, S., Talele, S.G., Thombre, N., Ahire, B. and Keservani, R.K., 2022. Oral Health and Prebiotics. *Prebiotics and Probiotics in Disease Regulation and Management*, pp.291-309.
56. Ahire, E.D., Sonawane, V.N., Surana, K.R., Talele, S.G., Talele, G.S., Kshirsagar, S.J., Khairnar, S.J., Thombre, N.A. and Mahajan, S.K., 2023. Preventive Measures of Type 2 Diabetes via Nutrition. In *The Metabolic Syndrome* (pp. 71-99). Apple Academic Press.
57. Keservani, R.K., Kesharwani, R.K., Vyas, N., Jain, S., Raghuvanshi, R. and Sharma, A.K., 2010. Nutraceutical and functional food as future food: a review. *Der Pharmacia Lettre*, 2(1), pp.106-116.
58. Keservani, R.K., Sharma, A.K., Ahmad, F. and Baig, M.E., 2014. Nutraceutical and functional food regulations in India. In *Nutraceutical and functional food regulations in the United States and around the world* (pp. 327-342). Academic Press.
59. Singh, P., Kesharwani, R.K. and Keservani, R.K., 2017. Antioxidants and vitamins: Roles in cellular function and metabolism. In *Sustained energy for enhanced human functions and activity* (pp. 385-407). Academic Press.