A Review on: Design of Polyherbal Formulation for Metabolic Disorders

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ABSTRACT: Metabolic disorders are generally defined as assemblage of contingencies which includes various diseases like dyslipidemia and excess abdominal fat, increase in sugar amounts in blood ("hyperglycemia"), impaired insulin utilization, long term inflammation also other diseases which exist in an individual and leads to various complications. Herbal plants are well known and utilized in various traditional medical practices to treat metabolic diseases as these contain various phytoconstituents and chemicals which possess therapeutic benefits to treat body ailments. These plants with another is used in synergistic blends to make polyherbal preparations to produce intensified effect rather than using a single plant which provides a better way to treat and manage metabolic disorders. In various traditional medicine systems it has been described that out of over 1300 herbal plants which are used for the diabetes cure most of them are also effective to treat other problems associated with metabolic disorders like dyslipidemia, oxidative stress, chronic inflammation and hypertension. The herbal plants played a significant role in plant based medicines in both traditional and modern healthcare systems. Most of the currently market available pharmaceutical products are developed by using these plants. The research on the therapeutic and biological actions of the herbal plants is increasing in detail due to their various benefits with relation to vitality & well-being.

Index Term - Metabolic Disorders, Polyherbal, Phytoconstituents, Dyslipidemia, Hyperglycemia and Insulin resistance.

INTRODUCTION

Overview of Metabolic Disorders

Metabolic disorders are defined as multifaceted abnormalities that consolidates of comorbid pathologies with various worries like risks of heart attack and stroke, renal and ocular diseases.[1] Metabolic disorders which include diabetes mellitus, oxidative stress dyslipidemia are leading causes of morbidity and mortality globally these diseases also leads to chronic problems like heart diseases, renal and ocular diseases and also other diseases.[2] World Health Organization (WHO) states that the non-communicable diseases is the main cause for the majority of global deaths and metabolic disorders contributing significantly to this problem. The expanding occurrence across both developed and developing nations highlights the crucial need for active protective and therapeutic approaches.[3] The speedy increase of metabolic diseases is closely connected to profound changes in eating habits, lifestyle choices. Diet, physical activity and food environments are main reasons for initiation to progress in disorders linked to metabolism multiple factors are responsible for such diseases like genetics, heritage, culture, puberty and other environmental issues.[4] Development, financial growth, and globalization have changed traditional nutritional practices into poor nutrition eating patterns. In most of the low and middle-income nations, as well as India, a nutritional shift is obvious defined as the consumption and intake of excessive amounts of fractionated lipids, sugar-sweet drinks also junk-food products.[5] At the same period, physical laziness and sedentary lifestyles further increases the risk of metabolic diseases. This change has resulted rise in the cases of obesity, diabetes, and cardiovascular problems, even in the younger population.[6] Metabolism is generally breaking down of food, in a very proper way by the human body into smaller components like proteins, carbohydrates, and fats. Metabolic disorders progress when ordinary metabolic processes are troubled. The major kind of metabolic disorders are diabetes mellitus, obesity, dyslipidemia, insulin resistance and metabolic syndrome. Many efforts are made over the last era to utilize herbal plants for treatment of body ailments. Majorly active agents of drugs have close connection with natural sources.[7]

Global Prevalence and Burden

Metabolic disorders signify a rising global health challenge, with substantial increases in occurrence, morbidity, and healthcare costs globally. Recent data reveals the concerning trends in disease burden across all age groups and geographic regions worldwide. Metabolic disorders generally occur due to various changes which further leads to occurrence of various diseases.[8] Starting from previous few years it has been observed that occurrence of such metabolic diseases is alarming far reaching issue. Demographic groups across nations is burdened from the problem of obesity or overweight and this is the main reason for metabolic diseases.[9] Studies illustrate that the most of the global population is suffering from the hyperglycemia which contributes to large number of mortality cases. So this is also a global issue which occur due to bad lifestyle and eating habits.[10] It is expressed by raised levels of glucose in the blood which occurs due to reduced insulin secretion which retards the glucose molecules absorption to use as a source for energy in the body and increases the risk of multiple diseases. Studies shows that the incidence rates are 10.91% and 26.3% for the cases of hyperglycemia or diabetes mellitus. It has been estimated that 27.4 million people older than 20 years are suffering from hyperglycemia.[11]A research states that most of the global population will suffer from diabetes mellitus if it is not controlled in a proper way. [12] Insulin resistance another metabolic disorder which leads to increased levels of glucose in the body.[13] Insulin resistance means inability of the cells in the body for utilization of this hormone properly. It has been approximated that more than 10% of the worldwide adult population is suffering with insulin resistance.[14] Dyslipidemia means improper levels of lipids in the body which causes various heart related issues.[15] Studies has shown 1 in 3 adults globally suffer with dyslipidemia which further leads to various heart and health problems.[16] Oxidative stress is a disorder which is triggered by high and abnormal production of oxygen reactive species and the body is unable to eliminate such species.[17] There are various studies which shows that the abnormal and high production of reactive oxygen species leads to initiation of multiple problems and oxidative stress is closely linked to various diseases which affect most of the world population and leads to morbidity and mortality and even death.[18] Chronic inflammation is defined as slow, long-term inflammation and widely regarded as common reason of mortality. Various organizations like WHO lists chronic problems for wellness as a main risk. Furthermore diseases associated with chronic inflammation is expected to increase determinedly for the next years globally.[19] Most of the population globally are suffering with these metabolic disorders affecting the health status, morbidity and mortality so it is important to improve the lifestyle, eating habits and more to overcome this burden globally.

Limitations of Conventional Therapy

Metabolic diseases are becoming gradually ubiquitous with a major effect on public health globally. Main problems linked with disorders of metabolism are hyperglycemia, dyslipidemia, oxidative stress, insulin resistance and many more.[20] The people with diseases associated to metabolism are checked if there is rise in glucose levels in the body, dyslipidemia and overweight.[21] Hyperglycemia affects about 200 million people globally and hyperglycemia patients have obesity-related issues. Major group of people is suffering from hyperglycemia shows distinctive attributes which are closely linked to metabolic disorders. So the Development of good pharmaceutical products to target such diseases is highly difficult.[22] In depth the current approaches to manage metabolic disorders are not effective which needs a better way to target such disorders.[23] Separately from the metabolic irregularities inflammation linked with these disorders also leads to heart problems and many other diseases.[24] The current conventional therapies has many drawbacks like side effects, less effective for long term use. Main therapeutic method for the management of such disorders is by changing way of living habits and doing proper exercises which can be beneficial. Furthermore these lifestyle changes are not sufficient to regulate such problems and which needs a better solution like combined medication approach.[25] Combined medication approach and poly-medication also have various issues and needs optimization to be made effective and operative.[26] A possible solution to poly-medications in the treatment of disorders linked to metabolism involves to develop better medication system by using two or more drugs. Subsequently the interest to formulate drugs to manage such issues is progressing to develop pharmaceutical preparations which will provide a best method of healing.[27], [28] On the other side the conventional treatments involve numeral therapeutic drugs and each drug is used and address a different aspect of the disease. The treatment by these medicines characteristically have negative side effects and have less effectiveness for the long term use. So the polyherbal preparations which are generally mixtures of various medicinal plants are evolving as attractive alternatives because of their medicinal benefits which aims multiple metabolic-pathways for the management of metabolic disorders. These polyherbal formulations offer possible benefits to cure numerous ailments in the body. Polyherbal treatments possess the synergistic effects of bioactive compounds.[29]

Rationale for Herbal and Polyherbal Therapy

Herbal plants are widely utilized and valued for wide range of uses in various traditional medicinal system due to their medicinal properties which are produced from plants and plant extracts. To improve the total health and well-being herbal medicines were known from ancient times for healing several sickness in the body which means that they act on various pathways and systems inside the body.[30] Single herbal therapies are widely used to treat and manage one or more diseases but polyherbal therapies are crucial section in which various plants are utilized for various diseases treatment with synergistic effect as described in historical books, scriptures and manuscripts of herbs with medicinal properties.[31] In general, polyherbal formulations involve the combination of many herbs into a single medicine. The theory of synergism states that the combined effect of several herbs is more than the benefits of each herb alone so the idea of polyherbal formulations emerged by this idea. Polyherbal therapies are designed to improve therapeutic efficacy, minimize toxicity, side effects and to treat various diseases in a better way.[32] Polyherbal formulations are very effective when it comes to the treatment and management of metabolic disorders which include insulin-resistance, hypertension, dyslipidemia, hyperglycemia, oxidative stress and chronic inflammation.[33] The ancient knowledge and modern scientific research serve as the basis for making the effective use of polyherbal preparations for medicinal purposes. The use of polyherbal therapies is well recognized among practitioners of traditional medicine because of the benefits of mixing specific herbs to treat complex diseases.[34] According to the studies conducted in few years suggest that the polyherbal formulations are safe and effective to treat acute and chronic diseases. The idea that polyherbal therapy have the possibilities to be a substantial addition to the therapies for metabolic disorders is brought to light by the knowledge of traditional and scientific study.[35]

PATHOPHYSIOLOGY OF METABOLIC DISORDERS

Insulin Resistance (IR)

Resistance to insulin occurs when the cells of human body system fails to respond efficiently to insulin leading to decreased glucose absorption. It is often linked to excess body weight, low physical activity levels, and other metabolic disorders. (IR) occurs as complicated problem which is associated to diabetes mellitus (T2D).[36] The various reasons like fatique, smoking, anxiety, diet, exercise are known to have an impact on this malady. It is also known as hyperinsulinemia in which the hormone is not able for binding to its receptor, which is basically an alteration in the insulin receptor itself of one or both of its downstream effector molecules, or a combination of these factors. It is a complex condition which is more qualitative than quantitative.[37] The main cause of insulin resistance in the obese people is supposed to be the receptor down regulation that follows insulin binding. The genetic features of insulin resistance may not have received much attention and is less studied. Various chromosomal regions were associated to fasting insulin levels, greater triglyceride and lower HDL cholesterol levels conferring to some human genetic research studies.

1. An irregular beta cell secretion product, (type A) due to:

a) Mutation in structural gene for insulin important for the creation of biologically defective molecules.

b) Improper conversion of proinsulin to insulin.[38]

2. Type B insulin antagonists which may be or could not be hormonal and are in the blood. Among the known hormonal antagonists which are group of various internal secretion may be reason of this clinical syndrome of insulin resistance in acromegaly. Among the non-hormonal antagonists are anti-insulin and anti-insulin receptor antibodies. Exogenic insulin is the cause of antibody production even if some individuals develop antibodies on their own.[39]

3. A target tissue or cell defect in insulin action (type A). This can be a post-receptor or a receptor failure. Obesity, T2D, and acromegaly are conditions which leads to loss of these receptors.[40]

Hyperglycemia

The pathophysiology of hyperglycemia (Diabetes mellitus) includes a complex interaction of several factors that affect insulin causing multiple diabetic complications.

1. Blood sugar regulation by insulin

In human body when the food is taken it increases the levels of glucose in the body. When these levels rise it triggers the release of insulin. This hormone enables the cells and tissues to utilize the glucose as a source of energy.[41]

2. Weak insulin sensitivity

It occurs when cells do not respond well to insulin leading to declined glucose absorption. The liver, skeletal muscles, and adipose tissue are key contributors to the development of this metabolic impairment. It is often linked to excess body weight, little physical activity and other metabolic disorders and represents a defining feature of type-2 diabetes.[42]

3. Improper functioning of pancreatic cells

It happens when the pancreas is not capable of generating enough insulin. In type 2 diabetes this disfunction manifests as insufficient insulin secretion, changes in the normal pulsatile pattern of insulin release and a reduced reaction to glucose levels. As the disorder progresses, beta-cell function continues to decline, resulting in lower insulin output and a gradual worsening of high blood glucose.[43]

4.Role of Inflammation

Inflammation is considerable reason for the initiation in hyperglycemia. Low-level inflammatory progressions contribute to both reduced insulin sensitivity and impaired beta cell activity.[44]

Dyslipidemia

Dyslipidemia is defined condition of improper lipids amounts which can be a basis for cardiovascular diseases. Numerous diseases occurs due to this. The heart problems generally like attacks and stroke occurs when the bad cholesterol which is known as LDL gets deposited inside the artery walls and limits the flow of blood leading to contraction and cause various issues. It has been shown in multiple researches and studies that the inadequate and unhygienic diet, high smoking and less exercise also contributes to the progression of this disorder so by changing such habits the health quality can be made better.[45], [46], [47]

Oxidative Stress

The disruption in the creation and disposition of unbalanced free radicles ("reactive oxygen species'') is termed as oxidative stress. These are basically small molecules and occur autonomously. Moreover these radicles are harmful and leads to oxidations and reductions. [48] The inception of these reactive species is multiplied by many folds during abnormal complications. There are diverse reactive species which are involved in oxidative stress which are produced by mitochondrial and microsomal electron transport chains.[49] Further more extreme amounts of reactive species leads to cellular damage and also initiates the development of multiple diseases.[50]

Chronic Inflammation

The reaction of the defense in the body to various injury, irritation, infections caused by pathogens, exposure to radiations and high to low temperatures, and autoimmune problems is known as inflammation. Hence it is described as the process of removing damaged cells, irritants which cause discomfort. Inflammation that remains for longer duration of time in the body is known as chronic inflammation.[51]

The pathophysiology of chronic inflammation involves various factors which leads to inflammation.[52], [53], [54], [55], [56]

1.Inflammatory Mediators

Chronic inflammation comprises of several chemical messengers which interact with each other and send signals which additionally leads to inflammatory response.

2.Cytokines

These are usually minute proteins which are produced by the immune system and play substantial roles behind the (inflammation). These cytokines leads to accumulation immune cells to inflamed tissues and modulate various reactions which occurs due to the inflammation.

3.Chemokines

Chemokines are also a type of cytokines and these significantly direct the movement of immune cells of the body to various sites of inflammation. The role of chemokines is vital in the conservation of chronic-inflammatory conditions.

4.Inflammatory Cells

The leading cells in chronic inflammation include macrophages, lymphocytes (mainly T cells), and plasma cells. Macrophages can migrate between the inflammation initiating, reducing states which induces consequences associated with chronic inflammation.

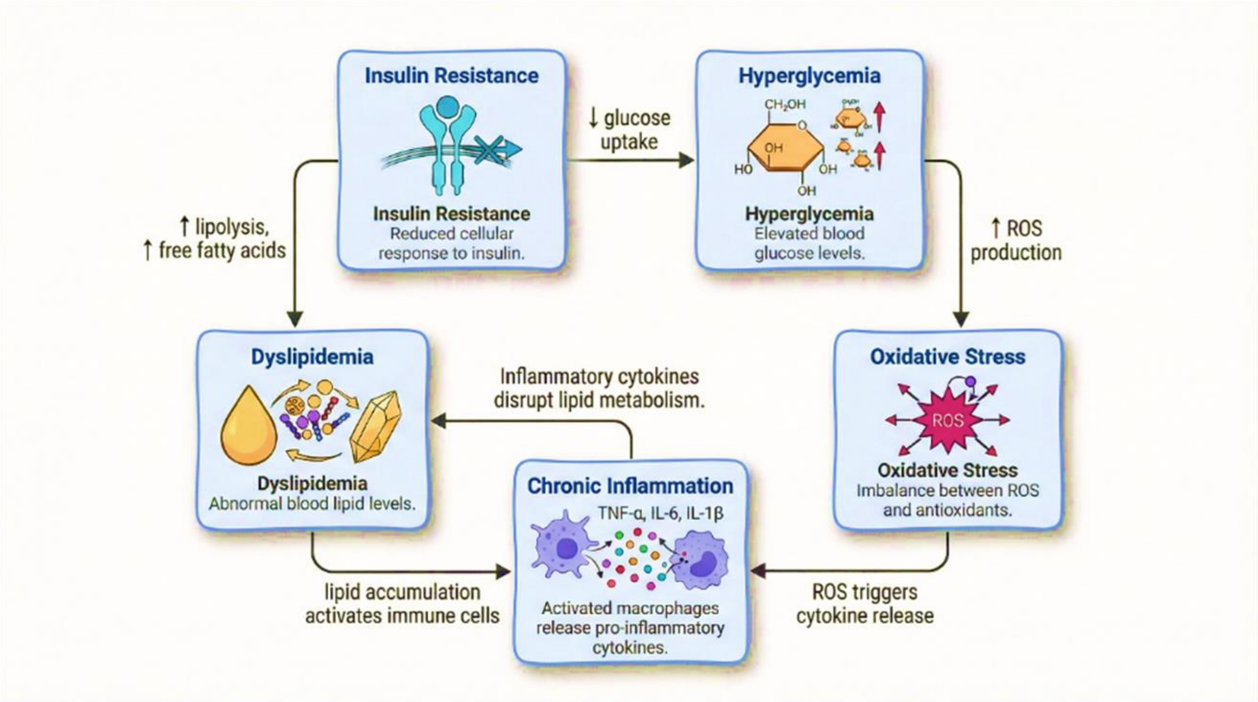

Figure 1: Interconnected Pathophysiological Mechanisms in Metabolic Disorders

CONCEPT OF POLYHERBAL FORMULATIONS

Definition and Principles

Polyherbal formulations are those formulations combining multiple herbal plants and their extracts. These are based on simple and basic principles which are stated in ayurveda system. Since ancient or historic era, the herbs are considered vital because of their protective effect on human health for numerous diseases. The use of several herbs for healing and curing illnesses is called polyherbal pharmacy. Modern studies describes that such formulations are highlighted and valued for their various health and restorative benefits. These formulations are widely utilized by humans throughout globally because of the fact that such preparations possess less toxicity and side effects in comparison to allopathic ones. The medicinal herbs contains various active chemicals which are attributed to diverse medicinal effects and can be effective in treating different diseases.[57], [58]

Advantages of Polyherbal Combinations

Polyherbal combinations have numerous advantages in comparison to single-herb preparations or conventional medications.[59], [60], [61], [62]

1.Synergistic effects: Polyherbal combinations may produce a synergistic effect, where the overall joint effects of the herbs are superior than the effects of individual herb alone. This can lead to improved therapeutic efficacy.

2.Multiple therapeutic effects: Polyherbal combinations can aim several disease pathways and have diverse therapeutic effects. This can provide a wider range of therapeutic benefits and help to manage multifaceted health conditions.

3.Lower toxicity: Polyherbal combinations can decrease the risk of toxicity and side effects connected with single herbs by means of lesser doses of each herb while maintaining therapeutic effectiveness.

4.Personalized medicine: Polyherbal combinations can be personalized to specific needs based on the detailed health condition and symptoms.

Concept of synergism

Synergism in polyherbal formulations is well-defined as the result where the two or more plant constituents interact to give a total higher therapeutic effect exceeding the individual effects of a single. The existence of this improvement is accredited to the fact that the various phytochemicals interrelate with codependent biological pathways leading to an increase in efficacy, reduction in toxicity and bioavailability.[63] Pharmacodynamic synergy is defined as the synergy among herbs that acts on the same biological target. Another phenomenon named biopharmaceutical kinetics takes place when a herb alone upsurges the (“ADME”) processing of drug in the body of some other herb therefore increasing systemic availability and therapeutic effectiveness.[64] All these mechanisms explain the efficiency of polyherbal preparations over single-herb preparations in complex diseases. Interactions between herbs may be additive, synergistic and antagonistic founded on the collective effect of two or more herbs. Synergistic interactions result in an increased therapeutic outcome than the estimated additive effect which is a positive herb-herb interaction which further improves bioavailability. Antagonistic interactions weakens the therapeutic activity which is the incidence of one herb conflicting the action of another or making opposition in the metabolic or receptor positions.[65] The importance of these relations helps to understand to develop operative polyherbal formulations with better safety profile and efficacy and tells us how to evade adverse effects.

Challenges in Polyherbal Formulation

Polyherbal formulation are generally combinations of two or more herbal plants consisting of various phytoconstituents when these constituents are collectively combined together to make a formulation it may show improved action.[66] Another associated concern is plant-derived bioactive substances which exist in herbs as these can react with each other and can affect the safety and efficacy of the formulation so it is necessary to check the compatibility between herbs before making any herbal formulation.[67],[68] In India maximum ayurvedic medications are mass-produced and sold outside the country. The order, act and guidelines for preparation of such products are not properly mandated.[69] It has been calculated that thousands of plant based products are listed in various systems in the country ("India''). In addition there is some negligence in providing and obtaining authorization for the production and sale of such medications which are derived from herbal plants. So these are some of major challenges which are associated with polyherbal formulations. [70]

SELECTION CRITERIA FOR MEDICINAL PLANTS

Phytochemical Profile

Phytochemical profile of herbal plants essential step towards the discovery of better drug candidates as it provides knowledge about the plant primary and secondary metabolites present in them. Herbal plants contains broad ranging natural compounds which are known for their various health related merits. According to fundamental concepts, Phytochemical profiling includes the organized identification and quantification of the bioactive complexes which are characterized into key and supplementary derivatives.[71] Evaluation methods advancements led to revolution for phytochemical profiling which enables researchers to detect and describe complex mixtures of plant metabolites with better accuracy and precision.[72] The dependence on herbal plants for drug discovery and development is associated with many issues. Inconsistency of compounds found in healing plants occurs by atmospheric and geographical aspects positions noteworthy problems for adjustment and reproducibility in research. These problems justifies the need for the multidisciplinary approach by adoption of latest evaluation methods along with computational tools to improve the therapeutic potency of medicinal plants efficiently. Phytochemical profile studies reveals a complex collection of major and minor agents in therapeutic plants. studies executed on Withania somnifera (Ashwagandha) have shown the presence of withanolides exhibiting anticancer, antioxidant, enhance immunity also many plentiful effects.[73]

Pharmacological Activities

The selection of herbal plants which are mostly known safer and affordable in comparability to man-made drugs are harnessed from historical era for health related illnesses. The largest health organization ("WHO'') estimates that majorly human race is relying for the cure of their body diseases on naturally plant derived medications because these are remarkably safer and economically viable to the synthetically made drugs. Formulations derived from the herbal plants consist of numerous healing actives which in contrast has pharmacological benefits for diseases which takes place inside or outside the body. [74], [75] Furthermore the prevalent theories are described in multiple medicinal books and states that one herb when used additionally with another they both may be more effective for various diseases.[76] Formulations developed by using healing ("herbal'') plants exhibit broader curative effects corroborated by systematic findings with experimental observations the pharmacological and therapeutic benefits include anticancer, anti-hyperglycemic, anti-microbial, antifungal ,antioxidants immunomodulatory, antihyperlipidemic, antihypertensive, cardioprotective, anti-inflammatory.[77]

Safety and toxicity profile

Safety and toxicity assessment is essential for polyherbal products because sometimes the interaction between several herbs may leads to impulsive results, variations in potency and even collective toxicity which is a main parameter to choose advantageous herbal flora.[78] Acute toxicity assessment is used to determine the immediate adverse effects after one high dose administration that will help in establishment of the lethal dose and safe initial doses in humans for use. The subacute trials offer the effect of repeated dosing with 28 to 30 days which provides a better understanding of the chemical, hematologic and histopathological changes. Chronic toxicity studies takes time about 80 to 90 days or more to recognize cumulative toxicity such as carcinogenicity, reproductive effects as well as metabolic interruptions.[79] The herbs alone can be considered a safe way but the interaction of the synergy between phytochemicals can leads to an increase in toxicity or variation in pharmacokinetics. So, the toxicity testing helps to determine safe dosage ranges and organ detailed risk as well as long-term safety profile. The utilization of polyherbal products is increasing globally so it is necessary to verify safety to promise protection to the health of the people.[80], [81]

MEDICINAL PLANTS USED IN METABOLIC DISORDERS

Gymnema Sylvestre

Gymnema sylvestre is a gentle species with a slow rate of growth and it can be located in different Asian countries. This plant occurs as a densely branched, woody plant that may climb to the top of trees. This plant falls under the botanical family of *Asclepiadaceae* often identified as madhunashni.[82] This plant is young in nature and consist of axis with bough which are leaped and leaves 2.5-6cm in length including conical root.[83] Gymnema sylvestre is defined in the treatment for urinary disorders and diabetes mellitus in the ancient medical manuscript of Sushruta Samhita. According to the traditional Ayurveda and homoeopathic systems of medicine it occurs as a beneficial flora with several medicinal actions like it is known to cure malaria, snakebites, asthma, amenorrhoea, leukoderma and so on.[84] Each and every part of this herb is highly potent as mentioned in traditional medicinal systems for cardioprotection, digestion related issues, lowering down sugar levels and many other body related concerns.[85]

Figure 2: Gymnema Sylvestre[86]

Momordica Charantia

Therapeutic formulations developed by the utilization of herbal plants has displayed a significant rise in few years because of lesser side effects on human health in comparison to synthetic medicines which are available in the market these drugs comes with the risks of side effects and toxicity.[87] Momordica charantia is mostly famous with other names like bitter squash, balsam pear, cerassee also karela in hindi it is included in the family of *Cucurbitaceae* and can be easily found in the regions of Asia, S.A(south America), Africa. [88] The plant contains a bitter tasting fruit which is basically utilized as food in various cultures. The fruit of this plant is highly rich in nutrients like vitamins, minerals and phytochemicals which further contributes to various health benefits. Momordica Charantia comprises of various chemicals which are triterpenes, proteins, steroids, alkaloids, saponins, flavonoids these chemicals are biologically active and have medicinal properties like promotes digestion, support liver and heart health, aids in weight loss, enhances immunity, antitumor.[89] It exists as trailing plant which may reach heights upto 14-15 feet in length. Studies demonstrated that Momordica charantia is an essential plant beneficial to control and manage D.B (“Diabetes mellitus’’).[90]

Figure 3: Momordica Charantia[91]

Trigonella foenum-graceum

Fenugreek scientific name is Trigonella foenum-graceum which pertaining to the family of *Fabacecae* and recognized as methi in accordance to various languages like hindi, punjabi & marathi.[92] This advantageous plant is grown and cultivated in winter season most predominantly in india and other Asian nations for their seeds.[93] There are multiple types of this plant (species) and the exact figure is not yet recognized properly.[94] Fenugreek (“Trigonella foenum-graceum’’) contains various phytoconstituents like alkaloids, saponins, polyphenols, flavonoids, lipids, carbohydrates.[95], [96] Due to the presence of these phyto-chemicals fenugreek show potent and promising benefits to manage multiple problems like atherosclerosis, dyslipidemia, beriberi, mouth ulcers, bronchitis, tuberculosis, chronic coughs, baldness, cancer, Parkinson's disease, hyperglycemia and for various metabolic disorders.

Fenugreek also has various pharmacological qualities such as a hypoglycemic, hypercholesterolemia, gastroprotective, anti-oxidant, laxative, appetite stimulation. Hence, it is considered as very beneficial plant to maintain and improve the health. Fenugreek seeds is generally employed in cooking either food preparations because of the traditional use for spices also the interest on these spices are also growing to for nutraceuticals for better human health and wellness.[97], [98], [99], [100]

Figure 4: Trigonella foenum-graceum[101]

Curcuma Longa

Haldi ("Curcuma longa") alternatively turmeric is a rhizomatous herb which is identified by various appellations haridra, manjal, pasupu, yellow ginger and grouped under family of *zingiberaceae* this herb is very potent and believed in different medicinal systems for its broad range activities. [102] Turmeric is also used as a culinary spice and broadly studied in scientific research. The plant is identified by its orange-coloured, tuberous rhizomes. The genus includes about 70 species and agriculturally cultivated in southern areas of Asia. In ancient medicinal practices turmeric is employed to diverse range of diseases and viewed as acknowledged natural remedy.[103] The major bioactive constituent curcumin has attracted important scientific interest because of notable positive health effects and good safety profile. In general curcumin exhibits substantial potential due to proven pharmacological activities which are antibacterial, antidiabetic, anticancer effects.[104], [105] Curcumin act on multiple molecular signalling pathways affecting different pathological pathways.[106] Turmeric contains wide range of related phytochemicals known as curcuminoids, among which curcumin is the major and most active compound. Turmeric extracts typically consist of curcumin in the highest proportion, demethoxycurcumin and bisdemethoxycurcumin.[107] Curcuminoids have established beneficial effects on metabolic regulation by enhancing insulin sensitivity, lowering sugar amounts and lessening inflammation.[108], [109]

Figure 5: Curcuma longa[110]

Cinnamomum verum

Cinnamomum verum in general is a valuable plant which is categorized within the family *Lauraceae* and referred to "true cinnamon tree" it is harvested and produced in multiple countries which include Srilanka, Brazil, Madagascar, India (Karela & Tamilnadu) to obtain dry bark.[111][112] Cinnamomum verum is a traditional herbal plant utilized in several civilizations owing to variety of curative effects. Cinnamon bark has different odour that is both aromatic and pleasant with somewhat spicy and little sweet flavor and consist of various phytoconstituents such as essential oil, major of them are cinnamaldehyde, cinnamyl acetate, eugenol, caryophyllene, linalool.[113] Cinamomum verum is helpful to enhance health by providing benefits including improves cardio & brain health, supresses inflammation, maintains good metabolism.[114], [115] In the Chinese system of medicines bark of this tree is believed for nerveprotection. [116] also consumed in raw form or powder by mixing in water to stabilize sugar levels inside the body. [117]

Figure 6: Cinnamomum verum[118]

Emblica Officinalis

Recent investigations indicates most of the citizens worldwide are utilizing herbal based preprations indicating hasty increase in usage of herbs. Emblica officinalis is often identified as amla, amalak, nellli and usiri in many tribal tongues moreover it contains various chemical substances which are beneficial for the good health and wellbeing.[119] Medicinal usage of this plant is highly valued in Ayurveda system of medicine due to its therapeutic properties. Emblica officinalis appertains to *Phyllanthaceae* family and also be found in multiple countries like Nepal, Srilanka, China, Malaysia nurturing in loamy soil with high drainage in warm conditions.[120][121]Emblica officinalis modest in size having height (8–18) meters length with leaves are simple with light greyish bark , greenish-yellowish flowers, and soft yellow fruits with six trigonal seeds.[122] Amla comprises of various types of biologically active phytoconstituents such as vit-C, tannins, natural acids, pectin fiber, polyphenols etc.[123] Emblica officinalis is highly beneficial to offer better health because of therapeutic attributes like promotes skin and hair vitality, removal of toxins, enhances eyesight & immune function, declines inflammation, manage ageing related issues, intensify energy levels in body. [124], [125]

Figure 7: Emblica officinalis[126]

Table 1: Common Medicinal Plants Used in Metabolic Disorders

S. No	**Plant Name**	**Family**	**Part Used**	**Major Phytoconstituents**	**Pharmacological Activity**	**References**
1.	Gymnema Sylvestre	*Asclepiadaceae*	Leaves	Triterpene saponins , from A to D (“Gymnemic acids”), flavonoids, triterpenoids, gurmarin, tannins, phenol based constituents, alkaloids, gymnemaside, inositole, lupeol.	Antimicrobial, antidiabetic, anti-inflammatory, anti-obesity, anti-cancer, hypolipidaemic, anti-helmenentic, free radical scavenging activity,	[127], [128], [129], [130], [131]

					antiarthritic, hepatoprotective, gastro protective.	
2.	Momordica Charantia	*Cucurbitaceae*	Fruit	Heteropolysaccharides such as (arabinose & mannose), A to G (momordicoside), 1 to 2 (momordicin), charantin, catechin, epi-catechin, luteolin, P-(polypeptide), MAP-30, cucurbitacines.	Antidiabetic, anticancerous, antimicrobial, antioxidant, antiviral, antimalarial, antihelmintic.	[132], [133], [134], [135], [136]
3.	Trigonella foenum graceum	*Fabaceae*	Seeds	Saponins, alkaloids majorly Trigonelline, Flavonoids, phenolics, Diosgenin, Mucilage, 4-Hydroxyisoleucine (amino acid), soluble fiber (Galactomannan)	Antidiabetic, antilipidemic, antifungal, antibacterial, anti-cancer, anti- obesity, cardioprotective antioxidant, gastroprotective, and antirheumatic and others.	[137], [138], [139], [140]
4.	Curcuma longa	*Zingiberaceae*	Rhizomes	Curcuma longa entail of various chemicals such as Curcumin I (demethoxycurcumin), Curcumin II (bisdemethoxycurcumin), and Curcumin III (curcumin), turmerone, Sesquiterpenes such arturmerone and β-turmerone.	Anti-inflammatory, anti-diabetic, antioxidant, anticancer, antimicrobial, neuroprotective, anti-viral, anti-dermatophytic, hepatopeotective, promotes heart health.	[141], [142], [143], [144]
5.	Cinnamomu m Verum	*Lauraceae*	Dried bark	Procyanidins (a,b), linalool, camphene, vanillic ,cinnamic and ferulic acids, coumarin, mannitol, cinaamaldehyde-e etc.	Hypoglycemic, Hypolipidemic, Antiviral, antitumor promotes heart health and stomach health.	[145], [146], [147], [148]

6.	Emblica officinalis	*Phyllanthaceae*	Fruit	Vit- C (ascorbic-acid), polyphenols, and tannins, nor sesquiterpenoids, punigluconin, phyllantine & phyllantidine, corilegin, phyllembein.	Pain reducing, antistress, antimutagenic, decreases fever, dyslipidemia control, enhance recovery of injuries.	[149], [150], [151], [152]

PHYTOCHEMICAL CONSTITUENTS AND MECHANISM OF ACTION

Alkaloids

The notation (alkaloid) relates to the organic nitrogenous substances present in the ecosystem isolated from microbes (bacteria or fungi) and flora. Alkaloids posess various biological properties contributes to prevention and control of multiple health conditions.[153], [154] Alkaloids are synthetically obtained from amino acids which result in various chemical structures and is generally isolated from variety of plants. The existance of alkaloids inside herbal species makes them responsible to act as supplementary constituents and provide protection against planteaters which promotes the growth.[155], [156] Alkaloids have alkaline characteristics due to which they are water soluble under acidic settings and lipid soluble under basic settings. From medical and therapeutic perspective the alkaloids are well recognized for their therapeutic attributes like anaesthetics, analgesic, anticoagulant, anthelmentic.[157], [158]

Flavonoids

Flavonoids are the compounds that exist in various parts of plant. Flavonoids are considered as vital pigments and these occur with chlorophylls and carotenoids in various plants. These compounds are recognized to give scent and taste to fruits, vegetables, flowers, and seeds.[159] Flavonoids are small molecular weight polyphenolic phytochemicals which are generally secreted as secondary metabolites in the plants.[160] According to various studies it has been estimated that about 10,000 types of various flavonoids have been identified and the number is also expected to increase because of the expanding curiosity in this field of research further flavonoids are classified into different subgroups and classes including flavaone, chalcones, iso-flavnoids, dihydro-flavanols, aurones.[161], [162] studies designate ingesting foods with higher amounts of such constituents holds variety of health benefits.[163] Furthermore, flavonoids possess various medicinal properties like antioxidants, mental-suppourt, regulation of metabolism, cardiac (heart) health enhancement, hepatic support.[164], [165]

Saponins

Saponins are broadly distributed in nature(“medicinal-plants’’) typically seen in green leaves, pulses, staple crops, roots & flowers.[166], [167] Saponins are formed in plants as they possess several actives which provides defense from predators and other benefits too. Saponins moreover exhibits health promoting benefits like protect cells and tissues from harms, support normal sugar amounts, enhances body immune functions, improves gut health.[168], [169], [170] Saponins further involves utilization for making herbal products in cosmeceutical field.[171] These phytochemicals (“saponins’’) holds emphasized expanded demand in consumer sector to synthesize various herbs derived formulations.[172], [173]

Polyphenols

Polyphenols are defined as naturally occurring compounds which are generally produced by plants.[174] These compounds consist of various aromatic phenol like structures. Polyphenols appear in plentiful amounts within the plants and these compounds are involved to tempt the biotic pollenating vectors which assists in pollination as well provides protection to the plants against U.V radiation, infective agents and herbivores. We intake polyphenols in our regular life because it exists in fruit crops, veggies, nuts, seeds, tree barks, flowers and other parts. [175], [176] The polyphenols has gained interest for research as various studies reported their health benefits and ability to control, provide immunity to fight various abnormalities in humans like aging, cancer, elevated sugar levels (“diabetes mellitus’’), cardiac issues.[177], [178] The food industries are also very interested in making food products and health supplements by utilizing the plants which contains high amounts of polyphenols for better health and wellness.[179]

MECHANISTIC PATHWAYS IN GLYCEMIC CONTROL

Insulin activity pathway: When we consume any meal the hormone (“insulin’’) is secreted by pancreas (beta cells) whose primary function is to initiate the uptake of glucose by the cells and tissues as energy to carryout numerous bodily activities. The (IRSinsulin receptor signalling substrate) with (P13K- phosphotidyl inositol-3- kinase) are regarded as the main targets for developing new medications which can be beneficial to regulate the glucose/sugar levels and aids in controlling it. [180], [181]

AMPK pathway: Initiation of this route involves major significance for regulating the energy utilization in the cells. AMPK is general regarded as (adenosine monophosphate activated protein kinase) which enhances assimilations of glucose, degradation of triglycerides and mitochondrial biosynthesis and all of these collectively leads to improved insulin sensitivity. So, the AMPK pathway targeting is regarded as beneficial approach to formulate many drugs that will improve the health of patients suffering from hyperglycemia.[182]

Gut hormone (GLP-1) process: Human body possess increatin messengers which secretes insulin to balance the glucose rates so that it cannot gets high too much and reduces the appetite. Hence exploration of novel GLP-1-based therapies or medications by focusing on this pathway signifies an innovative area for further research with noteworthy potential for better glycemic control.[183]

Ppar and adiponectin route: It serves the role like controllers ("peroxisome-proliferator activation receptor") and tells the body the way to efficiently store and use fat, sugars also adiponectin regulator produced by the energy storing cells guides the system to stabilize sugar and bodyfat. [184]

Glycogen-regulation enzyme suppression: By focusing on specific catalysts ("gsk-3") which are involved to handle stored sugar and the utilization of it we may formulate drugs to balance high blood sugar. The Inhibition GSK3 action signifies potential therapeutic approach for better glycemic control and reducing hyperglycemia.[185]

Table 2: Major Phytochemical Constituents and Their Mechanisms in Metabolic Disorders

S. No	Phytochemical Class	Major Compounds	Natural Sources (Examples)	Mechanism of Action in Metabolic Disorders	Therapeutic Effect	References
1.	**Alkaloids**	Berberine	Berberis aristata (Daru haridra) and other berberis species	It can help to reduce blood glucose by stimulating insulin responsiveness and decreasing the amounts of high fats within the blood.	Antihyperglycemic, Antihyperlipidemic	[186], [187]
		Trigonelline	Trigonella foenum graecum (Fenugreek), coffee beans	Improves and enhances insulin action through modulation of proteins and receptors in the hepatocytes and muscles and facilitates the glucose to enter the cells.	Anti diabetic, hypolipidemic	[188], [189], [190]
		Piperine	Piper nigrum (Black pepper), Piper longum	Boosts insulin sensitivity and decreases inflammation.	Anti-diabetic, Anti-obesity	[191], [192], [193]

2.	**Flavonoids**	Quercetin	Allium cepa (onion), Malus domestica (apple)	Reduces insulin resistance, strengthens sugar uptake & supresses glucose amounts inside blood.	Anti-diabetic, Anti-inflammatory and insulin sensitizing	[194], [195], [196]
		Naringenin	Citrus paradisi (Grape fruits) and citrus fruits	It regulates major pathways such as AMPK to improve insulin sensitivity, decreases lipid accumulation and reduces oxidative stress.	Hypolipidemic, Anti-obesity and Anti-diabetic	[197], [198], [199], [200]
		Kaempferol	Camellia sinensis (Tea), Brassica oleracea (Kale)	It acts by activating AMPK,SIRT pathways and increases the energy utilization, enhancing insulin sensitivity and also lowers lipids accumulation.	Anti-obesity, Anti-diabetic and lipid metabolism regulation.	[201], [202]
3.	**Saponins**	Diosgenin	Dioscorea villosa (Wild yam) and other species.	It acts on various pathways which improves insulin signaling, restores beta cell function of pancreas and lipase inhibition.	Anti-diabetic, hypolipidemic	[203], [204], [205]
		Gymnemic acids	Gymnema sylvestre (Gurmar)	Enhances insulin secretion and reduces glucose absorption in the intestine providing better glycaemic control	Anti-diabetic and improved lipid metabolism	[206], [207], [208]

				and helps in the effective management of diabetes also reduces lipids level in the body.		
		Charantin	Momordica charantia (Bitter gourd)	It acts as natural insulin which promotes insulin secretion, protects pancreatic cells also slows mechanism (gluconeogenesis).	Anti-diabetic	[209], [210], [211]
4.	**Polyphenols**	Resveratrol	Vitis vinifera (Grapes) and berries	It activates SIRT1 and AMPK which further improves consumption of energy sugars and curbs hunger.	Anti-obesity, Anti-diabetic	[212], [213]
		Curcumin	Curcuma longa (Turmeric)	It inhibits NF-κB, MAPK and other inflammatory pathways which leads to decrease in proinflammatory cytokines and reduces inflammation.	Anti-inflammatory	[214], [215], [216], [217]
		Chlorogenic acid	Coffea arabica (Coffee beans)	It acts by modulation of various inflammatory pathways leading to lessening (inflammation), slow down the absorption of sugars in intestine and burning of fat.	Hypoglycemic, inflammation-reducing	[218], [219], [220]

CLINICAL EVIDENCE SUPPORTING POLYHERBAL FORMULATIONS

Polyherbal formulations are defined as formulations containing two or more herbs and these are foundation of traditional medicinal procedures aimed to achieve improved therapeutic effects with lesser and lesser side effects by synergistic action.[221] There are various noteworthy areas of clinical evidences that shows that the polyherbal formulations are effective and safe for usage. Organized review on clinical trials stated that the polyherbal formulations when given to persons suffering from higher sugar levels has shown good outcomes.[222] Polyherbal formulations(PHF) in early and human/animal testing revealed possibilities and effectiveness for obesity management which is a condition associated with diabetes mellitus.[223] The idea of combining polyherbal extracts with allopathic medications is recognized as allopolyherbal formulations has also revealed potential in reducing the mandatory dose of allopathic drugs and decreasing the linked adverse effects and increasing the anti-diabetic effects.[224] Another study on polyherbal formulations using the extracts of herbal plants such as Cassia auriculata, Centella asiatica, and Zingiber officinale is studied for the antihyperlipidemic and anti-diabetic properties.[225]

According to a study on infectious diseases which is performed during the Covid-19 pandemic polyherbal medications have been investigated for their possible therapeutic benefits. Lianhuaqingwen (LH) capsule which is a Chinese herbal product has shown best favourable outcomes for people with coronavirus.[226] The dermatologic ("'skin') studies indicates health product consisiting (haldi-curcuma longa) decreased hypermia and swelling on facial area.[227] Another study on Triphala which is a renowned Ayurvedic formulation presented augmented wound healing properties when incorporated in advanced nanofibrous injury care dressings.[228]These studies indicates that the polyherbal formulations are effective and safe for human health and wellbeing as supported by various preclinical and clinical studies these studies also highlights the importance and effectiveness of polyherbal formulations over other treatments.

SAFETY, TOXICITY AND HERB–DRUG INTERACTIONS

Polyherbal formulations has gained interest globally because of their safety and effectiveness as a natural treatment for the various types of diseases. The safety, toxicity and herb-drug interactions are important considerations for making such polyherbal formulations and for their therapeutic applications. Though (PHFs) are appreciated for their potential to improve efficacy and safety through synergistic actions but it is necessary to do a proper assessment to verify their safety and efficacy.[229] Herbal medicines usefulness is tied to their documented benefits in many different medicinal treatises describing that these are greatly risk free and possesses lesser toxicity.[230] Most of the evolving nations are utilizing herbs and aromatic plants and their preparations for health care purposes. It has been found that about 25% of allopathic medicines are made from natural sources particularly plants which are majorly employed in primary healthcare.[231] The toxicological investigation is very vital for the develop of new drugs. The US regulatory authority ("FDA'')have specified that the conformation of new molecules for their toxicity profile and pharmacological action in animals to ensure that the new drugs should not be toxic for use.[232] Toxicity study is defined as a non-clinical safety assessment which is carried out to create information about the toxicological properties of various compounds. The main goal of the toxicity studies of any compounds is to check the safety of the chemical substances before they can be employed as test drugs during the procedure of clinical trials. Acute and subacute toxicity investigation of medicinal plants are the quickest ways for evaluating the toxicological nature of the phytoconstituents present in them .[233]

Herb-drug interactions happen when a conventional medicine is taken alongside with an herbal component which can change the drug pharmacological effects or vice versa. The consequence of the herb-drug interaction may amplify or decline effects and moreover the interaction may result to the appearance of a new effect which is not probable from using the drug or herb alone. It generally occurs when the patient takes the medication and herbs concurrently. So the use of herbs along with other drugs is raising concerns due to their interactions with each other which can be positive or negative or may leads to a new effect hence it is necessary to study the interactions properly for developing new products for validating biocompatibility and therapeutic efficiency.[234], [235]

REGULATORY ASPECTS OF HERBAL FORMULATIONS

In compliance with multiple organizations like global health authorities the medications which are made from herbs contains phytochemicals that holds benefits for good health. [236] Different findings states that all around the world the usage rate of such medications is high.[237] In general the botanically derived drugs are viewed less harmful with better efficiency for maintain health as herbal formulations demonstrate fewer or no sideeffects than allopathic drugs this is the major rationale for their use by most of the population.[238] Herbal formulations are regulated in india by various authorities which are NCISM("National commission for Indian system of medicine''), national medical research body (" ICMR-indian council of medical research"), Ayush ministry and various other bodies are also involved. Formulations which are prepared by utilizing medicinal herbs are controlled by D&C act and rules ("Drugs and cosmetic act 1940, rules 1945") it also regulates production, sale, high quality, import and export of herbal products.[239], [240]

FUTURE PERSPECTIVES AND SCOPE

Polyherbal formulations signifies a auspicious therapeutic value for metabolic disorders by utilizing the synergistic effects of various herbal plants to attain improved efficacy, reduced toxicity, and a multi-targeted method to multiple conditions like obesity, hyperglycemia, dyslipidemia, insulin resistance and many others conditions.[241], [242], [243] The future perspectives and scope of polyherbal formulations has various important characteristics which includes advanced standardization, mechanistic explanation, nanotechnological advancements, clinical validation and combining (PHFs) with digital health technologies also proper regulations are also important for their safe and efficient use. A noteworthy future challenge for herbal products involves achieving sturdy standardization by using advanced analytical techniques and control of quality. The conventional methods for evaluation of herbal products lacks the accuracy and precision of quality control.[244], [245] International health authority ("WHO'') formed standards, guidelines, methods to interpret various chemical constituents existing within the healing plants.[246] A major drawback of polyherbal formulations is poor bioavailability, low stability and irregular responses and such limitations associated with the polyherbal medicines can be managed and improved by nanotechnology which provides a better future approach by making nano formulations such as phytosomes, nanoemulsion and nanoparticles which provides improved stability and bioavailability for the herbal actives.[247], [248], [249] Studies have examined artificial intelligence models to foresee and design modified nanocarrier formulations for herbal drugs containing various phytochemicals which are used for treating several diseases linking phytomedicine and modern nanotechnology. These developments can ameliorate and improves the drug penetration, reducing dosage and minimizing the side effects.[250], [251] In detail, the scope of polyherbal formulations for metabolic diseases is growing swiftly and is supported by proper understanding of their multi-target activities, developments in drug delivery systems and rising demands of natural therapeutic products.

CONCLUSION

The design of polyherbal formulations for metabolic disorders signifies a better approach with understanding of traditional medical knowledge and modern pharmacological discipline to combat & tackle assorted disorders owing to anomalies related to metabolism also these all conditions are complex and multifaceted. Polyherbal formulation are generally based on the fact that they provides synergistic effects which improves the total effect of the formulation rather than using a single herb and target various pathways for effective and safe management of various disorders. Along with that, combining herbal extracts with low-dose allopathic drugs which is known as (allopolyherbal formulations) has also appeared as an approach for minimizing the drug dosage and linked adverse effects and sustaining the therapeutic effectiveness. Still, the complexity of PHFs possess noteworthy challenges in standardization and quality control because polyherbal formulations consist of numerous phytoconstituents. Standardization should also include biological activity assays like in vitro anti-lipase, α-glucosidase inhibition, and antioxidant capacity which provides data about the of therapeutic potential of the polyherbal formulations. In, conclusion a properly designed polyherbal formulation offers several advantages for the cost-effective and safe treatment of metabolic disorders with less side effects and toxicity. However, further research including clinical studies and regulatory standardization is important for the safety, efficacy and acceptance in modern healthcare for better health and wellbeing.

CONFLICT OF INTEREST

The authors have no conflict of interest regarding this investigation.

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