

## PHARMACOLOGICAL POTENTIAL OF POLYHERBAL FORMULATION KABASURA KUDINEER: A REVIEW

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### ABSTRACT

Diabetes is a long-term medical condition in which the body has difficulty converting food into energy. High blood glucose levels are produced by poor glucose management, which alters the overall metabolic process of the body. The accumulation of abnormal (excess) blood glucose and the inability to metabolize plasma glucose causes lethal damage to the body's major organs or organ systems such as heart disease, nephropathy, retinal degeneration, sensory loss, and even premature death. Despite the administration of long-term medications, available diabetes mellitus therapy is unable to cure and unable to prevent patients from key organ damage. Diabetics have a significant financial burden, in addition to drug-drug interactions. A tremendous amount of data and proof has been amassed, proving medicinal plants' enormous potential. Plants are a naturally occurring source of therapeutic strategy for mankind. In accordance with the literature review, people who have metabolic syndrome are more likely to contract COVID-19. To overcome pandemics, we need efficient and effective herbal management. Kabasurakudineer is a polyherbal formulation that is gaining acceptance in the medical world. It may have a synergistic impact that is advantageous in the therapy of metabolic illnesses such as diabetes. Type 2 diabetes is expected to affect 640 million people by 2040, with 70% of those affected being hypertensive and predisposed to obesity and dyslipidemia.

**Keywords:** KabasuraKudineer, Metabolic Syndrome, Diabetes Mellitus, Antidiabetic Drugs, Phytomedicine, Poly-Herbal Formulation.

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### INTRODUCTION

Metabolism is an important mechanism in our organs that allows us to generate energy and produce essential molecules. It encompasses catabolic and anabolic events that occur in the organism via several metabolic pathways. These actions also generate nitrogenous waste products, which are removed by the excretory system. An orderly metabolism is required to maintain cell milieu and general health. Irregularities in the body's metabolism itself result in numerous disorders like Obesity, Diabetes mellitus, Hypertension, and Gastrointestinal disorders. Lifestyle also plays an important role in maintaining good metabolism. Genetic predisposition, sedentary lifestyle, and faulty eating habits are some of the common factors that contribute to altered metabolism. Metabolic syndrome (MetS) is a bunch of chronic conditions associated with hypertension, hyperglycemia, hypoglycemia, extra fat around the abdomen, and excessive cholesterol or triglyceride levels. MetS increases the menace of diabetes, cardiovascular abnormalities, and organ failure. The projected incidence of type 2 diabetes in 2040 is around 640 million of which 70% of patients are hypertensive and prone to obesity and dyslipidemia. The ideal treatment for patients suffering from more than two indications is to have target-based combination therapy. Patient compliance becomes an issue when multiple drugs need to be taken on a long-term and possible drug-drug interaction. Phytochemicals are bioactive compounds originating from plants for various defense mechanisms. PHF formulations such as KabasuraKudineer (KSK) are pretty frequent. It is composed of 15 herbal ingredients that collaborate to produce a synergistic action. Throughout the Covid-19 and Swine flu pandemics, KSK was frequently recommended as flu and fever therapy. KSK is a Siddha establishment; the formulation is created in the form of powder, and the preparation obtained is known as 'choornam'.

Water is used as a solvent in the preparation of "Khadha." MetS (Metabolic syndrome) is a cluster of disorder, where energy utility and storage is affected, according to studies, almost a quarter of the global population is affected by MetS. MetS also referred to as 'Reaven's syndrome,' 'Syndrome X,' and 'Deadly quartet'. Individuals suffering from metabolic syndrome are mostly prone to coronary heart disease, hemorrhage, and hypertension. Population with MetS are at greater risk of cardiac abnormality as compared to others. Physical inactivity, fatness (overweight), Race, genetic factors, and aging are the major forces behind the increasing prevalence of MetS.<sup>1-4</sup>

### Diabetes

WHO (world health organization) is the one to publish the first distinction of diabetes-mellitus in 1980, and in modified form in 1985. The 1980 and 1985 include Insulin-dependent diabetes mellitus (Type-1) and non-insulin-dependent diabetes mellitus (NIDDM) are two types of diabetes mellitus (Type-2). Whenever the body would be incapable to synthesize adequate insulin, insulin-dependent diabetes mellitus (IDDM) arises. In such instances, patients are entirely reliant on an exogenous supply of insulin. Teens and young people have a higher incidence of IDDM.<sup>5</sup> Lethal damage in  $\beta$ -cells of the pancreas is reported in IDDM patients and categorized as an autoimmune disorder or idiopathic diabetes.<sup>6</sup> NIDDM (Diabetes Type 2) is the most commonly reported abnormality, that leads to cardiovascular disease.<sup>7</sup> NIDDM patients are not capable of responding to insulin which may be healed with changes in lifestyle including diet management physical activity, and therapeutic interventions. The inception is common in populations greater than 40 years of age with obesity. Both types of diabetes are associated with increased sugar levels in plasma, polydipsia, extreme hunger, Dysuria, weakness, fuzzy eyesight, etc. The etiology of diabetes mellitus is very complex according to many studies free radicals are the factor behind the physiology of Diabetes and its complications.<sup>8</sup> These free radicals are very much potent that can cause cellular molecular damage, leading to abnormalities in cellular activities. In fact, one of the most influencing factors of diabetes onset is the abnormal metabolism of lipids and oxidation of the lipoproteins through protein free radicals.<sup>9</sup> Glucose and extracellular peptide also get turned into glycoproteins which is a lethal complication in diabetes.<sup>10</sup> The electron transport chain (mitochondria),<sup>11-14</sup> membranes NADPH oxidase 15,16 are associated with reactive oxygen species (ROS) synthesis and are affiliated with insulin resistance and  $\beta$ -cell dysfunction of the pancreas.<sup>17</sup> AGEs (advance glycosylation end product) is the end product of protein (non-enzymatic glycosylation), leads to magnifying long-lived bio-molecules in cells, and causes cellular function abnormalities.<sup>18,19</sup> It also increases vascular permeability for micro as well as macro-vascular structures using specific macrophagereceptors. Nucleic acids "AGEs" cause abnormal gene expression leading to mutation. Oxidative stress coexists with a deterioration in antioxidant status in diabetes that might lead to negative effects from free radicals.<sup>20</sup> "Vitamins C and E" and some plant products are common natural antioxidants. These antioxidants are potent in reducing oxidation stress and significant oxidant activity, which is beneficial in diabetic control.<sup>21</sup>

### Antidiabetic Drugs

Regulation of blood sugar levels can control Diabetes mellitus by using different types of target-based therapeutic interventions, like physical activity, yoga, and a healthy diet. Insulin treatment and other oral hypoglycaemic medications "sulphonylureas, thiazolidinediones, peptide analogs" are in common practice these days.<sup>22</sup>

### Sulfonylureas

(Glipizide, glyburide, gliclazide, glimepiride) inhibit the "adenosine triphosphate-sensitive potassium channel (K-ATP)" in the pancreatic beta-cells causing altered membrane resting potential and influx of calcium. An influx of calcium stimulates insulin secretion by pancreatic beta cells.

### Meglitinides

(Repaglinide and nateglinide) the action of the mechanism is similar to Sulfonylureas i.e., regulation of adenosine triphosphate-sensitive potassium channel. But it acts on different pancreatic beta-cell receptors.

**Biguanides**

(Metformin) enhances “hepatic AMP-activated protein kinase activity” which reduces hepatic gluconeogenesis, lipogenesis, and increased glucose (insulin-mediated) uptake in muscular cells. Although the physiochemical potential of metformin is not fully explored, the drug is considered to be the front-line therapy for patients diagnosed with T2DM.

**Thiazolidinediones**

(Rosiglitazone, pioglitazone) stimulate peripheral glucose uptake, resulting in decreased hepatic glucose by the action of peroxisome proliferator-activated receptor gamma.

**Alpha-Glucosidase Inhibitors**

(acarbose, miglitol, voglibose) act on intestinal alpha-glucosidase enzyme and prevent digesting starch, inhibits the reabsorption of carbohydrate, and regulate glucose and fructose from sucrose. SGLT2 inhibitors (dapagliflozin and canagliflozin) inhibit 90% glucose reabsorption, and glycosuria in diabetic patients and lower the plasma-glucose level by inhibiting sodium-glucose co-transporter-2 (SGLT-2) in renal glomeruli (proximal tubules). DPP-4 inhibitors stimulate and prolong the action of glucagon-like peptide (GLP), by inhibiting glucagon release DPP-4 inhibitors increase insulin secretion and decreased gastric emptying, resulting in decreased plasma-glucose concentration. DPP-4 (dipeptidyl peptidase-4) is a pancreatic peptidase cleaver. ‘Glucagon-like peptide-1 (GLP-1) an insulin secretagogue, results in altered glucose homeostasis as well as type-2 diabetes. DPP-4 gained attention in the last decade as inhibitors of DPP-4 also called gliptins were launched as a new class of oral medication for diabetes mellitus (type 2). Several DPP-4 inhibitors are reported in clinical trials which are very potent against diabetes mellitus type 2, obesity, dyslipidemia, and hypertension.

**COVID-19 and Diabetes**

The coronavirus outbreak is dragging the world population like a dragon and causing health crises worldwide. COVID-19 is a viral pandemic triggered by a coronavirus in 2003, 2012 severe acute respiratory distress syndrome outbreak of coronavirus-2 (SARS CoV-2) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) engulfed a large population. Several cases of pneumonia infection with unknown etiology in “Wuhan City China” have been reported in 2019 and later on, the infection was transmitted to the whole world. “SARS-CoV2” predominantly causes respiratory instances which include flu-like and interstitial pneumonia symptoms. It rapidly leads to “acute respiratory distress syndrome (ARDS)” being lethal and requires ICU treatment.<sup>23</sup> However, other organs like the kidneys, liver, and heart are affected, and death is reported due to multi-organ failure. Among COVID-19 symptomatic patients, older age, metabolic syndrome diabetes, adiposity, hypertension, acute disruptive pulmonary disease (ADPD), cardiovascular disease (CVD), malignancy, and immunodeficiency are all high fatality risk variables.<sup>24,25</sup> Studies have enlightened that diabetes and other metabolic syndrome have a huge risk of various infections, post-infection, complications, and mortality; symptomatology is a commonly reported factor for high prevalence in COVID-19 patients. Hypertension and diabetes mellitus are the most prevalent symptomatology. Coronary heart disease, cardiac failure, obesity, and cerebrovascular disease are commonly associated with non-Asian patients infected with SARS-CoV2.<sup>26</sup> Hyperglycemia-associated metabolic imbalance facilitates viral entry and infection of cells in a retrospective, a multicenter study from China (Hubei) reported that patients’ normal plasma glucose levels had comparatively lower rates of death and fewer complications with individuals with abnormal plasma glucose levels.<sup>27</sup> SARS-CoV2 directly affects metabolic organs, and pancreatic beta-cell, and leads to the onset of hyperglycemia and sudden deterioration of the pre-existing hyper or hypoglycaemic condition.<sup>28</sup> It is strongly recommended that COVID-19 patients maintain adequate glycaemic control, and potential interfering effects of antidiabetic medications including metformin, glucagon-like peptide-1, and sodium-glucose-co-transporter 2 inhibitors receptor agonists affiliated with dehydration have been highlighted.<sup>29</sup> Anti-hyperglycemic, lipid-lowering, as well as anti-hypertensive drugs, which are commonly prescribed to treat diabetic patients, have indeed been implicated in COVID-19 due to their pleiotropic potential on inflammation, but there is no affirmation that these antidiabetic drugs have a major contribution in disease amelioration or attempting to prevent life-threatening illness. However, a

study claims that regular diabetes medicine, which includes renin-angiotensin system (RAS) blockers as well as dipeptidyl peptidase-4 inhibitors, has no impact on clinical severity (DPP-4).<sup>30</sup> Another case-control COVID-19 hospitalizations study in Italy found no significant effect of DPP-4 inhibitors.<sup>31</sup> Literature indicates, diabetes mellitus is not an element of danger for COVID-19, though it shows a noxious effect. The impact of diabetes mellitus has been shown in Fig.-1, further studies are needed to explain the action mechanisms of disease severity of diabetic compared to non-diabetic.

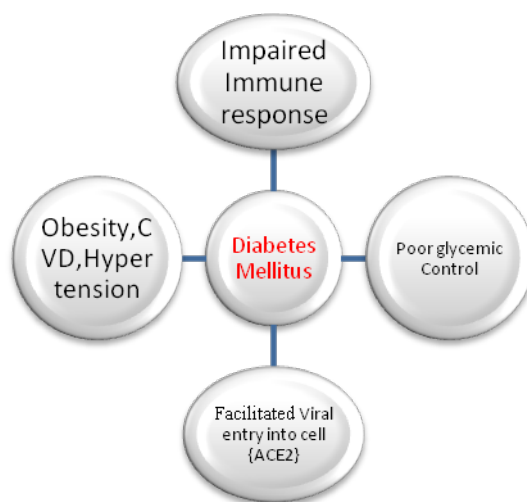


Fig.-1: Impact of Diabetes Mellitus

### Herbal Remedy for Diabetes

The therapeutic use of the medicinal herb as the conventional medication is as old as our civilization. Such healthcare is referred to as Herbalism or Botanical medication. Diabetes/metabolic syndrome and herbs have a long relationship. The ethnobotanical report proves herbs are a potent source of anti-diabetic drugs. Many herbs may have anti-diabetic properties of which some are clinically proven to possess anti-diabetic properties. We have a glorious history of conventional medicinal plants used for therapeutics in various acute and chronic infections such as diabetes, cancer cardiac abnormality, etc. “Charka Samhita and Susruta” an Indian-based ancient scripture explain the phytopharmacology of diabetes and its complexities.<sup>32</sup> Sickness, swelling, vomiting, diarrhea, alcohol flush, migraine, malignant anemia, and values of these parameters have all been associated with synthetic anti-diabetic medications, which are widely recommended for the treatment of diabetes. Herbal formulations are a better choice than synthetic medications since they are more readily available, have fewer side effects, and are less toxic. When there are no other treatment options available certain conditions or chemical medications are inadequate, these herbal formulations as standardized extracts are used. Synthetic pharmaceuticals do not provide a permanent cure for diseases such as diabetes, cancer, or other lifestyle conditions such as dyslipidemia or hypertension, whereas herbal drugs do. Allopathic medications are chemically synthesized herbal and natural products, whereas herbal formulations are plant-based organically created products.<sup>33,34</sup>

### Traditional Plant-Based Anti-Diabetic Drugs

Herbs and medicinal plants are commonly used as standardized extracts. Many Clinical studies confirm that medicinal plant has anti-diabetic and restorative properties for pancreatic  $\beta$ - cells.<sup>35</sup> Some polyherbal formulations against diabetes available in the market (Table-1).

Table-1: Herbal Drug Having Anti-Diabetic Properties

Brand name	Company name
Diabcon	Himalaya
Diasulin	Himalaya
Pancreatic Tonic 180 cp	Ayurvedic herbal supplement
Diabeta	Ayurvedic herbal health product
Diabecure	Naturebeaytesanté

Epinsulin	Swastik formulation
Dia-care	Admark Herbal limited

### Phytomedicine

Various plant Varieties and herbs are used for medical benefits, and their uses refer to as “Medicinal plants”. “Herb” originates from “herba” and “herbe”. A Latin word, and a French word respectively. Hippocrates “Father of medicine,” said: “Let thy food be thy medicine, and thy medicine shall be thy food”. Plants are food, health, and healing remedies providers and we must be so grateful to the plants that are being used as drugs and as various healing modalities for various infections, physical illness as well as mental and emotional imbalances. India's medical systems include 'Allopathy,' 'Ayurveda,' 'Siddha,' 'Unani,' 'Yoga,' 'Naturopathy,' and 'Homoeopathy'. While Homoeopathy was first established in the 1800s and afterward acknowledged as part of Indian medical systems, it has become extensively incorporated into Indian culture and enriched, just like any other conventional healthcare system.<sup>36</sup> These methods were maintained in many ways, including the exorbitant cost of treatments, the detrimental consequences of several synthetic agents, the emergence of resistance, insufficient drug distribution, and a rapidly shrinking population density. Drug resistance to routinely used synthetic pharmaceuticals for contagious diseases is increasing, leading to greater utilization of plant ingredients as public health remedies. These days use of herbal medicine in the Ayurveda medical system is the major source of health care globally. Almost one-fourth of drugs used in the pharmaceutical industry are derived from herbal sources. WHO pointed out herb-based medical systems as a crucial building block for basic health care in India and China.<sup>37</sup> Figure-2 represents the advantage of Phytomedicine.

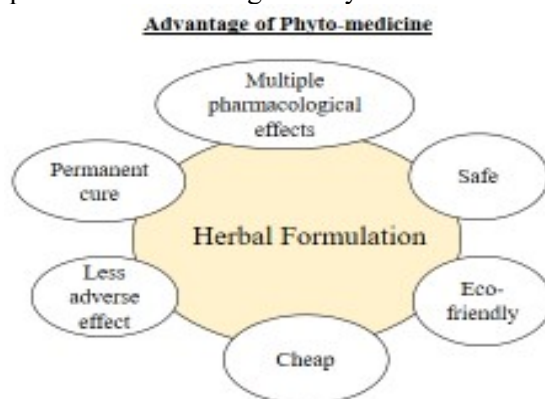


Fig.-2: Advantage of Phytomedicine

### “Poly-herbal” Formulation

The formulation of Drugs in Ayurveda follows basic two principles (a) Using a single drug and (b) using a mixture of more than one drug. Polyherbal formulation (PHF) relates to the use of more than one medicine. This critical conventional therapeutic herbal approach utilizes the combination of medicinal herbs to attain extra therapeutic efficacy and is termed polyherbalism and polypharmacy. The ayurvedic document “Sarangdhar Samhita” has pointed out the concept of polypharmacy in which plant formulations and mixed plant extracts are having better efficacy rather than individual plant extract. Currently, ayurveda creates a variety of dosage forms, the most prevalent of which is PHF. Active phytochemical molecules of individual plants are usually present in trace amounts and they are unable to provide therapeutic advantages. According to authoritative sources, these plants possess synergistic capabilities when it is used together and produce a stronger result than when used separately. The discovered therapeutic activity could be additive or synergistic.<sup>38</sup> Herb-herb interaction in a formulation is termed synergism. Active herbal constituents are significant only when they are in PHF, but not evident when used alone in certain pharmacological actions. Herbs combinations such as ginger and blackpepper or *pepper longum* enhance mucous-reducing effects, ginger, and neem positively control any maximal effects, the mixture of cumin, black pepper, and asafoetida down-regulates bloating due to digestion abnormality, and Guduchi and turmeric are commonly used as an immunity booster.<sup>39,40</sup> Pharmacodynamics and pharmacokinetics are two mechanisms of how synergism acts. Pharmacokinetic synergism deals with the ability to facilitate metabolism (absorption, distribution, and elimination).

Pharmacodynamics collegiality on the other side is the investigation of active metabolites exhibiting similar pharmacological interventions that engage the same receptor and physiological system. Aside from that, it is hypothesized that complications and a combination of circumstances are the leading causes of disorders with observable and unobservable symptomatology. At the very same medication, a polyherbal formulation may impact several domains.<sup>41</sup> The Synergic, effect (polyherbalism) gives out some additional benefits which are not shown by a single botanical product. It is indisputable that enhanced medicinal advantage can be gained by the use of poly-herbal formulation (PHF). Dose management of the PHF is crucial to perform a prudent pharmacological response and to abate the risk of adverse effects. Besides, the Good-naturedness of PHFs provides more comfort to patients by eradicating more than one single composition at a time, which offers better pharmacological possibilities concomitantly. All these potentials of PHF ensure the acceptance of PHF over individual plant formulation. Now, these days so many different PHFs have been merchandise, which is clinically proven and show desired therapeutic activities. Some examples are listed in Table-2.

Table-2: Poly-Herbal Formulation

PHF (company)	Herbs used	Uses	References
Dihar (Rajsha Pharmaceuticals, Ahmedabad, India)	<i>Enicostemma littorale</i> , <i>Momordica charantia</i> , <i>Embelica officinalis</i> , <i>Gymnema sylvestre</i> , <i>Tinospora cordifolia</i> , <i>Curcuma longa</i> , <i>Syzygium cumini</i> , <i>Azadirachta indica</i> .	Used for the hyperlipidemia treatment	41
Diabet (Herbal Galenicals, India)	<i>Coscinum fenestratum</i> , <i>Curcuma longa</i> , <i>Phyllanthus reticulatus</i> , <i>Strychnos potatorum</i> , <i>Tamarindus indica</i> , <i>Tribulus terrestris</i> .	Antidiabetic	42
Vidakana Choornam	<i>Embeline</i> , <i>Moringa oleifera</i> , <i>Piper longum</i>	Beneficial for liver disorders (Jaundice and steatosis)	43
Bharangyadi	<i>Clerodendrum serratum</i> , <i>Hedychium spicatum</i> , <i>Inula racemosa</i>	Antiasthmatic	44
Kabasura kudineer	<i>Zingiber officinale</i> Rosc, <i>Piper longum</i> , <i>Syzygium aromaticum</i> , <i>Tragia involucrata</i> L, <i>Anacyclus pyrethrum</i> , <i>Hygrophilla auriculata</i> , <i>Terminalia chebula</i> , <i>Justicia adathoda</i> , <i>Anisochilus carnosus</i> , <i>Saussurea costus</i> , <i>Tinospora sinensis</i> , <i>Clerodendrum serratum</i> , <i>Andrographis paniculata</i> , <i>Sida acuta</i> , <i>Cyperus rotundus</i>	Fever, Respiratory disorder, Swine Flu	45

### Kabasura kudineer

Kabasura kudineer (KSK) formulation is a very common example of PHF. It consists of 15 herbal ingredients (Table-3), which have a synergic effect. KSK was recommended frequently throughout the pandemic of Covid-19 and Swine flu as medication for flu and fever. KSK is a Siddha establishment, the formulation is prepared in the form of powder, where integral or specific plant (plants) parts are pulverized into crude powder and the preparation obtained is termed as 'choornam'. "Khadha" is prepared by using water as a solvent and heating till volume decreases to 1/4th to 1/8th of its initial volume, commonly such khadha is known as kudineer.

Table-3: Ingredients of Kabasura Kudineer

S.No.	Plant name	Parts
i	<i>Zingiber officinale</i> Rosc	Rhizome
ii	<i>Piper longum</i> L.	Fruit
iii	<i>Syzygium aromaticum</i>	Bud
iv	<i>Tragia involucrata</i> L.	Root
v	<i>Anacyclus pyrethrum</i>	Root

vi	<i>Hygrophillia auriculata</i>	Root
vii	<i>Terminalia chebula</i>	Fruit
viii	<i>Justicia adathoda</i>	Leaf
ix	<i>Anisochilus carnosus</i>	Leaf
x	<i>Saussureacostus</i>	Root
xi	<i>Tinospora sinensis</i>	Stem
xii	<i>clerodendrum serratum</i>	Root
xiii	<i>Andrographis paniculata</i>	Stem, Leaves
xiv	<i>Sida acuta</i>	Root
xv	<i>Cyperus rotundus</i>	Rhizome

It is then filtered and the filtrate is used for therapeutic purposes. One can take three to four times a day dose of 30 ml before the meal, Prepared KSK is to be used within 3 hours of its preparation. During the preparation of the Khadha "Decoction" method is used where the major phytoconstituents do not undergo any considerable change like other conventional formulations. Figure-6 and 7 give an insight into a number of plants v/s Pharmacological potentials and their Phytochemicals.

### ***Zingiber officinale***

Ginger is an edible herb commonly cultivated in South and East Asian countries. Its color varies from light yellow to brown.<sup>45</sup> Volatile oils, gingerol, and diarylheptanoid chemicals are all found in *Zingiber officinale*. It is a widespread ingredient in food and pharmaceuticals, but it also has a lot of aesthetic potential.<sup>46</sup> Ginger has been recognized as a feed supplement by the FDA in the United States. Zinger has a spectrum of medicinal characteristics, comprising anti-diabetic, anti-oxidant, and anti-inflammatory properties. Ginger rhizome is commonly used as a culinary ingredient and also has traditional medicinal value.<sup>47</sup> The ginger extract significantly reduces fasting plasma glucose concentration in diabetic rats. Reduced alanine, aspartate aminotransferase (ALT and AST) levels, alkaline phosphatase (ALP), cholesterol, and liver total lipid were observed. Increased levels of triglyceride and liver glycogen were observed with respect to the placebo group.<sup>48</sup> Ginger is used in the management of various abnormalities like muscular pain, various cancers, inhibition of cell-cycle progression, apoptosis, metastasis, etc. It has anti-inflammatory and immune responses. Hexane fraction of rhizome extract inhibits the synthesis of PGE-2, NO, TNF- $\alpha$ , IL-1 $\beta$ .<sup>49-52</sup>

### ***Piper longum***

*Piper longum* is a common spice and flavoring material frequently used in our kitchen for cooking. Various studies revealed that it is a potent agent for the management of tuberculosis. Gonorrhea, an arthritic condition can also be treated with this.<sup>53,54</sup> Piperine can enhance the pharmacokinetics of various drugs including rifampicin sulfadiazine, phenytoin, streptomycin, tetracycline, and other drugs. Its pharmacokinetic effect enhances the absorption of drugs, resulting in fewer adverse side effects.<sup>54,55</sup> Major phyto-molecules of *Piper longum* are sterols, piper, legumin, piperine, pippalartin, and glycosides. Piperine and piperlartine have a significant effect on tumor weight. The anti-bacterial and anti-fungal activity of *Piper longum* against pathogenic microbes was also reported. In another study, the apoptotic and antioxidant activity of *P. longum* is reported by using DPPH ASSAY, and TUNEL ASSAY. This property of Piperine makes it a potent anti-cancer agent.<sup>56,57,58</sup>

### ***Syzygium aromaticum***

*Syzygium aromaticum* belongs to the "Myrtaceae" family. The clove tree is composed of leaves and buds, bud appears only after 4 years of the plantation. Clove has anti-bacterial, anti-viral, anti-carcinogenic, and anti-fungal potentials. It is a commonly used antimicrobial and antioxidant agent. Its use has been reported in various industries like the perfume industry, soaps, and detergent industry, dental pain, tooth infections, burns, and wounds.<sup>59,60,61,62</sup> *Syzygium aromaticum* extract shows antimicrobial activity against MRSA, *B. subtilis*, and *S. typhi*. Cloves are also used in the therapy of nausea, vomiting, and stomach discomfort and act as nerve boosters. In tropical Asian countries and in America, it is used to diminish microbial infections like malaria, tuberculosis, and cholera.<sup>63,64,65,66,67,68,69,70,71,72,73</sup> In vivo study in diabetic

rats had established that nutritional supplementation of clove extract re-establishes the levels of the antioxidant enzyme to reduce lipid peroxidation and reverse hyperglycemia to normoglycemia.<sup>74,75,76,77,78</sup> Nutritional supplementation of clove extract re-establishes the levels of the antioxidant enzyme in diabetic rats. The potential is about 85% - 92% of the total oil concentration. Clove oil in combination with rosemary oil has demonstrated antibacterial activity against *P. aeruginosa*, *B. subtilis*, *S. aureus*, and MRSA probably through a synergistic effect. The antifungal efficacy of clove oil towards various species of fungus is well documented.<sup>79-91</sup>

### ***Tragiainvolucrata***

Extracts of *Tragiainvolucrata* in petroleum ether, chloroform, and acetone extracts are potent to impede *E. coli* growth. Alcohol extracts were potent in reducing the growth of *Pseudomonas aeruginosa* and *Vibrio cholera*. The compound shell sol was very effective against in vitro cultures of *Staphylococcus aureus*. Extracts from roots exhibit antifungal activity against *Malassezia furfur* and *Trichophyton rubrum*.<sup>92,93,94,95</sup> When shellsol was fed to rats (dosage 50 µg/kg body weight) complete healing was observed after 24 days. This finding justifies the use of *T.involucrata* as a wound-healing agent. The aqueous and methanol extracts were experimentally proved to have these properties in animal models.<sup>96</sup>

### ***Anacyclus pyrethrum***

*Anacyclus pyrethrum* commonly known as Akarkara has a significant role in ancient Ayurveda and the herbal medicinal system. The root of the *Anacyclus pyrethrum* is beneficial in the treatment of diseases such as diabetes and microbiological infections. In alloxan diabetic rats, the root extract demonstrates a reduction in blood glucose levels without producing hypoglycemia. In vitro, the antioxidant activity of *Anacyclus pyrethrum*'s ethanolic extract was demonstrated and the extract was effective in scavenging the hydroxyl-radical OH and hydrogenperoxide. Phenolic phyto-compounds of extract mediate this activity. The root extract shows an anti-bacterial effect on *Streptococcus aureus* and *Streptitis sanguis*.<sup>97</sup>

### ***Hygrophila auriculata***

*Hygrophila auriculata* is used to treat blood disorders, cancer, diabetes, bacterial infections, liver diseases, and hematopoietic disorders. It is used commercially in formulations to treat liver disorders, anasarca diseases of urogenital tract infections and diseases, gonorrhea, respiratory disease asthma, and dysentery. Organic extracts reduce plasma glucose as well as the down-regulation of peroxide radicals and TBARS (thiobarbituric acid reactive substances) in the kidney and liver. Extracts down-regulate lipid-peroxidation and up-regulate superoxide dismutase and catalase. The aqueous extract is effective in glucose tolerance and does not show any significant effect on gluconeogenesis or absorption of glucose in the intestine.<sup>98,99</sup>

### ***Terminalia chebula***

*Terminalia chebula* is randomly distributed throughout India, Burma, and Srilanka. The plant is used in the formulation "TRIPHALA" a formulation used for disorders like diabetes and epilepsy. *Tannin gallate* is on top priority in Ayurveda medicine, due to its remarkable capability of healing. Other than tannin, gallic acid, chebulinic acid, ethyl gallate, methyl gallate, glycosides flavonol, and tri-terpenoids. Tetra-O-galloyl-β-D-glucose and Penta-O galloyl-β-D-glucose were isolated and identified.<sup>100</sup> *Terminalia chebula* is useful for numerous purposes. Fruits provide anti-inflammatory capabilities and could be used as a mouth rinse, antitumor agent, and anti-astringent, for burn, and ulcer healing. Antioxidant properties are attributed to phenolic chemicals, which have been extracted from plants. The antioxidant property works as a liver booster.<sup>101</sup> Anti-bacterial compounds, Gallic acid, and ethyl ester are antibacterial compounds present in the alcoholic extract. It is also reported extract is well effective in stomach cancers, ulcers, and gastritis.<sup>101</sup> Phyto molecules and their phytochemical potentials have been shown in Fig.-3.

### ***Justicia adathoda***

*Justicia adathoda* is a traditional source of medicine and food for many ailments. Saponins present in extracts show antiprotozoal, antifungal, antiviral, anticancer, and cholesterol-lowering.<sup>102-107</sup> Leaf extract of *Adhatodavasic* showed antidiabetic activity and anti-inflammatory potentials. The alkaloids vasicine



and vasicinol inhibited sucrose activity. Leave extract has also shown antibacterial activity against *Streptococcus pneumonia*, and *Klebsiella pneumonia*.<sup>108-111</sup>

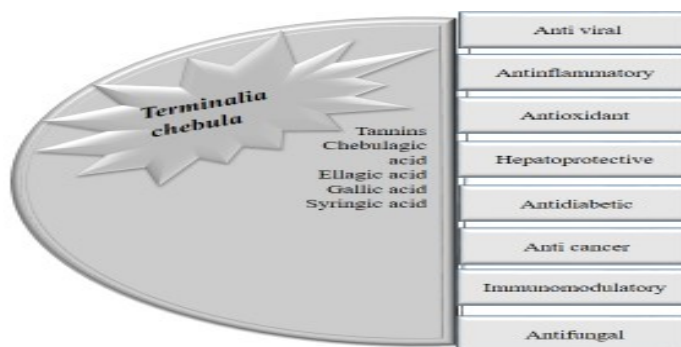


Fig.-3: Showing Phytomolecules and Phytochemical Potentials of *Terminalia chebula*

### *Anisochilus carnosus*

A “Lamiaceae” family member *Anisochilus carnosus* commonly known as karpuravalli and thick-leaved lavender, is an annual herb. Common phytochemicals present in the aerial parts of the herb are steroids, alkaloids, glycosides, flavonoids, and tannins. This herb has a long history of use in the healing of cancer<sup>112</sup>, inflammation, and fungal infection<sup>113</sup>, the leaf paste of *Ocimum sanctum* *Anisochilus carnosus*, *Alpinia galangal*, and *Mentha piperita* is much effective in dermatitis and influenza. The leaf extract was proved to have antibacterial and antifungal activities in the agar diffusion method against various<sup>114</sup> antioxidant properties, DPPH activity, and hepatoprotective activity due to its phenolic contents.<sup>115</sup>

### *Saussureacostus*

The genus *Saussurea* comprises about 300 species, with around 61 species found in India. *Saussureacostus* commonly called “costus” shows promising medicinal potential, and become a critically important herb. *Saussureacostus* (Falc.) Lipsch (Compositae), popularly known as Kuth in Ayurveda.<sup>116</sup> *Saussureacostus* is found in the sub-alpine of Himanchal Pradesh, Uttaranchal, and Jammu-Kashmir from altitudes of 3200-3800m. It is listed in the endangered category, according to the Indian government export of this herb in any form is an illegal activity. Its root extract is commonly used in the treatment of asthma as antispasmodic, cough, cholera, and rheumatism. Root extract can be taken as a single extract or in combination. N-butanol has shown anti-inflammatory potential by inhibiting pro-inflammatory cytokines secretion. It also promotes the synthesis of thymus-activated chemokine and macrophage-derived chemokine. The phenolic and flavonoids contents showed strong antioxidative potential by blocking DPPH radicals.<sup>117-118</sup>

### *Tinospora sinensis*

*Tinospora sinensis* is commonly known as Giloya or Guduchi found in India, Sri Lanka Myanmar, and China. Giloya is traditional Ayurvedic medicine and has diverse therapeutic potential. Figure-4 represents the phytochemicals and phytochemical potentials of *Tinospora sinensis*. Researchers suggest that this plant has enormous potential in current pharmaco-therapeutics. Diabetes Mellitus treatment by *Tinospora cordifolia* is a great option<sup>119,120</sup> for anemia jaundice, diabetes, chronic fever rheumatism, allergy, urinary disorder, skin diseases, inflammation, and relieves burning sensation, hyperacidity, and liver disorders like hepatitis.<sup>121,122</sup> Phosphorus, calcium, and protein are major constituents of plant leaves. Steroids, fatty acids, polysaccharides, glycosides, and diterpenoid lactones are other major compounds found in different parts of plants. *T. cordifolia* also exhibited antibacterial and antifungal activities.

Ethanol extract of the plant has the potential to increase the erythrocytes membrane lipid peroxide activity. The leaf extract was also reported for its antioxidant potential.<sup>123-129</sup> The root extract of *T. cordifolia* shows an anti-diabetic, anti-hyperglycemic effect by glucose-lowering effect. Antibacterial activity was improved against different strains of bacteria by the use of silver Nano formulation. Alkaloids present in the plant have insulin-mediated activity and secretagogue effects.<sup>130-146</sup>

### *Clerodendrum serratum*

*Clerodendrum serratum* is a Lamiaceae family with common names such as glory-flower, bag-flower, and bleeding heart. It can be found in both tropical and temperate climates, most frequently seen in tropical African and southern Asian countries. The aerial part of the plant when extracted in methanol it shows significant anti-oxidant properties.<sup>147</sup> Whereas phenol-extracted phytochemicals of leaves show dose-dependent scanning activity of DPPH. Prominent antioxidant (DPPH assay), and the radical scavenging activity is also reported.<sup>148</sup> Literature indicates its wide range of therapeutic potentials, which includes neuroprotective, hypoglycaemic, hepatoprotective, anti-oxidant anti-inflammatory, antimicrobial, and anticancer.

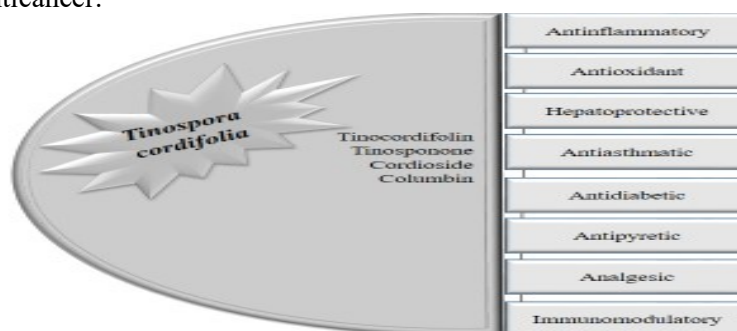


Fig.- 4: Phyto molecules and Phytochemical Potentials of *Tinospora sinensis*

Flavonoids and polyphenols are potent antioxidant molecules found in the different solvent extracts of the herb. Methanol extract of *Clerodendrum serratum* has antimicrobial activity against *Micrococcus pyogenes* and *Staphylococcus aureus*. The Methanol and chloroform extract, exhibit moderate action whereas stems ethyl-acetate extract has relatively greater anti-fungal and anti-bacterial potentials compared to tetracycline a standard drug.<sup>149-153</sup> Methanol extract shows significantly decreased "body weight, food consumption pancreatic lipase activity, glucose, insulin, total cholesterol (TC), serum glutamic pyruvic transaminase (SGPT) and low-density lipoprotein (LDL-c), triglycerides (TG) levels" in mice. The aqueous extract of leaves shows anti-adipogenic effect, hypoglycaemic and hypolipidemic. *C. phlomidis* methanol extract shows significantly decreased "body weight, food consumption pancreatic lipase activity, adiposity index, glucose, insulin, total cholesterol (TC), serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and low-density lipoprotein (LDL-c), triglycerides (TG) levels" in mice.<sup>154-158</sup>

### *Andrographis paniculata*

*Andrographis paniculata* is a conventional blood purifying booster in our country commonly known as green chiretta commonly found in India, Sri Lanka, and China. In chronic fevers and skin eruptions, it is frequently used as household medication. A diverse range of chemical constituents is present in this herb which includes flavonoids, diterpenoids, lactones, and glycosides. Its safety and efficacy in respiratory infections are proven in clinical trials. In vitro, antioxidant studies of organic extracts show significant antioxidant activity with respect to aqueous extract. The purified *Andrographis paniculata* extract decreases plasma-glucose, triglyceride, and LDL levels significantly in an animal model. Oral administration of the extract can prevent the induction of hyperglycemia significantly. Leaf has maximum antioxidant potential as compared to fruit and stem extracts. Organic extraction of leaves and stem have antimicrobial activity against various gram-positive and negative bacteria.<sup>159-163</sup>

### *Sida acuta*

*Sida acuta* a Malvaceae family member is an invasive weed. Its native habitat is in Mexico and Central America, but now these days can be easily seen in tropical and subtropical areas. The plant is also known for its spiritual practices.<sup>164</sup> Based on traditional knowledge plant is usually taken as preventive medication for snake bites, fever, diarrhea, and skin diseases. The therapeutic potentials of plants contain anti-plasmodial, antibacterial, and antioxidants. The plant is commonly used in combination with others in the polyherbal formulation as well as its crude extract is also used.<sup>165</sup> The screening of the Methanolic

Extract of *Sida acuta* reveals its significant antimicrobial activity on a variety of bacteria. The antimicrobial activity of the plant is probably due to the oxidation of phenolic compounds and alkaloids found in the extract of this plant.<sup>166,167</sup> Evaluation of *Sida acuta* extract of flower and leaf in combination proves its antimicrobial activity and revealed the potential of phenolic compounds and alkaloids, but the instability of phenolic compounds due to its nature of forming polymer in air through oxidation reactions is a big challenge to convert it in a potent therapeutic option because this oxidized concentration may result in toxicity and can lead adverse effect which is found in some cases.<sup>168-173</sup> Figure-5 represents phyto molecules and phytochemical potentials.

*Cyperus rotundus* is a perennial weed plant belonging to the Cyperaceae family, commonly known as Nagarmotha, purple nut sedge, or nut grass. Its native habitat is in Africa and Europe. Its medicinal and pharmacological potential is listed in our “Ayurvedic, Charaka Samhita”, and is commonly used in traditional medication globally for the prevention of a wide range of abnormalities and shows antibacterial, anti-diabetic, hepatoprotective, insecticidal, and anti-inflammatory. It also has immune and nutritive booster values.<sup>172</sup> Tuber and rhizomes of this plant are most important from the medicinal point of view. In the carrageenan-induced inflammation model, *C. rotundus* essential oils have shown anti-inflammatory action and it also shows its peripheral analgesic potential. Phenols and alkaloids are active phytoconstituents of *C. rotundus*. The aqueous and organic extracts of *C. rotundus* show their anti-obesity property.<sup>173</sup> *C. rotundus* essential oil and the alcoholic extract was demonstrated for their antibacterial and anti-fungal property.<sup>174-177</sup>

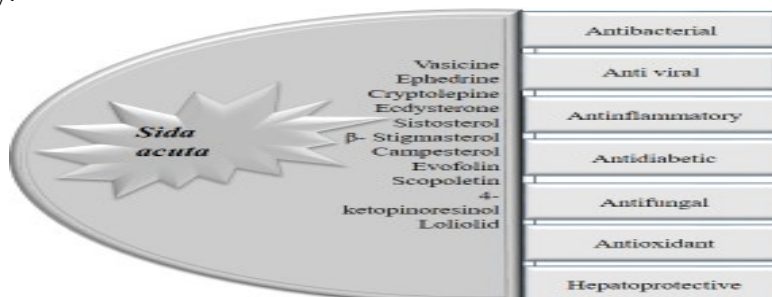


Fig.-5: Showing Phyto molecules and Phytochemical Potentials of *Sida acuta* *Cyperus rotundus*

Table-4: Major Phytochemical Class of Kabasura Kudineer Ingredients

Ingredients of Kabasura kudineer	Alkaloid	Flavonoid	Saponin	Tannin	Steroid	Terpenoid	Phenol	Glycoside	Starch	Amino acid	Fatty acid	Vitamin C	Essential oil	Volatile oil	Resin	Sterol	Anthraquinone
<i>Zingiber officinale</i>	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓		✓	✓	
<i>Rosca</i>	✓	✓			✓		✓			✓		✓		✓			
<i>Piper longum</i>	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓				
<i>Syzygium aromaticum</i>	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓				
<i>Tragia involucrate</i>	✓	✓	✓	✓		✓		✓	✓							✓	✓
<i>Anacyclus pyrethrum</i>	✓	✓	✓	✓					✓	✓			✓				✓
<i>Hygrophillia auriculata</i>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓	
<i>Terminalia chebula</i>	✓	✓	✓	✓		✓	✓	✓	✓			✓	✓			✓	
<i>Justicia adathoda</i>	✓	✓	✓	✓			✓		✓	✓	✓	✓				✓	
<i>Anisochilus carnosus</i>			✓	✓		✓										✓	
<i>Saussurea costus</i>	✓	✓		✓	✓		✓	✓									
<i>Tinospora sinensis</i>	✓			✓	✓	✓		✓	✓		✓		✓				
<i>Clerodendrum serratum</i>	✓		✓		✓	✓	✓	✓	✓			✓					✓
<i>Andrographis paniculata</i>	✓	✓	✓	✓	✓	✓	✓					✓					✓
<i>Sida acuta</i>	✓	✓	✓	✓	✓	✓	✓	✓									
<i>Cyperus rotundus</i>	✓	✓		✓		✓		✓	✓								

*Crotundus* extract has significant anti-oxidation activity and also inhibits aerophilic injury. Flavonoids and phenols are principal phytoconstituents of this plant which may have antioxidant potential, scavenging activity, and anti-hyperglycemic potential. The presence of various secondary metabolites makes it important and of great value for medicinal purposes.<sup>178-180</sup> Lists classes of phytochemicals and pharmacological potentials of various ingredients in Kabasura kudineer have been shown in Table-4 and Table-5 respectively.

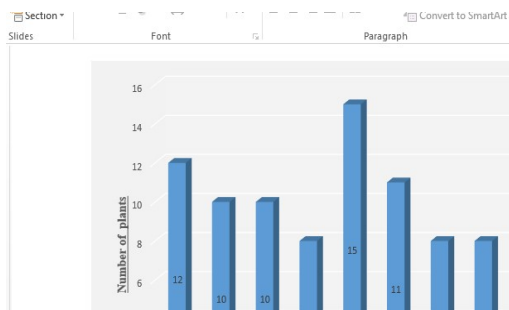


Fig.-6: Graph Showing Number of Plant v/s Pharmacological Potentials

Table-5: Pharmacological Potentials of Ingredients of Kabasura kudineer

Ingredients of Kabasurakudineer	Antibacterial	Antiviral	Antimicrobial	Antifungal	Antioxidant	Antiinflammatory	Antidiabetic	Immunomodulatory	Anti-cancer	Antiasthmatic	Neuroprotective	Analgesic	Antipyretic	Wound healing	Hepatoprotective
<i>Zingiber officinale</i> Rosc	✓	✓			✓	✓			✓	✓	✓				✓
<i>Piper longum</i>	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓			
<i>Syzygium aromaticum</i>	✓	✓		✓	✓	✓			✓	✓		✓			✓
<i>Tragia involucrate</i>			✓			✓	✓			✓				✓	✓
<i>Anacyclus pyrethrum</i>	✓	✓	✓	✓		✓	✓	✓	✓		✓				
<i>Hygrophillia auriculata</i>	✓		✓		✓	✓			✓		✓		✓		✓
<i>Terminalia chebula</i>		✓	✓	✓	✓	✓	✓	✓	✓						✓
<i>Justicia adathoda</i>	✓	✓			✓	✓			✓	✓	✓				
<i>Anisochilus carnosus</i>	✓	✓			✓	✓									
<i>Saussurea costus</i>	✓	✓	✓	✓		✓	✓		✓	✓				✓	
<i>Tinospora sinensis</i>					✓	✓	✓	✓		✓		✓	✓		✓
<i>clerodendrum serratum</i>	✓	✓			✓	✓									
<i>Andrographis paniculata</i>	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓		✓
<i>Sida acuta</i>	✓	✓	✓	✓	✓	✓	✓							✓	✓
<i>Cyperus rotundus</i>	✓	✓	✓			✓	✓		✓		✓	✓			

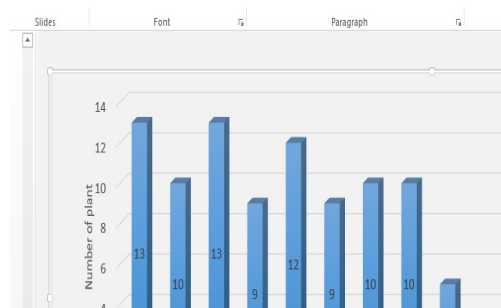


Fig.-7: Graph Showing the Number of Plants v/s Phytochemicals

## CONCLUSION

Diabetes is a most lethal metabolic syndrome. Its increasing prevalence is a big concern for the human population globally, therefore its management is of great significance. Diverse ranges of medication are frequently used to treat various diseases but none of them can be treated as safe, each of them has its own side effect. Researchers are continuously searching for alternate efficacious therapeutic options for the management of diabetes. In this direction, they found plants as a potent source. Kabasura kudineer a polyherbal formulation, is very common in practice these days, due to its potential to treat respiratory infections common cold, and flu. Ministry of Aayush is also recommending this, during the covid-19 pandemic in our country as a preventive “kadha”. As this formulation is composed of fifteen plant ingredients it can have a synergic effect which can be effective in the management of metabolic syndrome like diabetes besides its main use to date. Kabasura kudineer which has not been fully explored needs to examine its detailed activity as a potent anti-diabetic agent.

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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[RJC-8028/2022]