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TINOSPORA CORDIFOLIA AND ITS VARIED ACTIVITIES: WHAT IS BELIEVED AND WHAT IS KNOWN?

Madhav Mutalik[1], Maitreyee Mutalik[2]

1. Department of Pharmacology, Sir Seewoosagur Ramgoolam Medical College, Belle Rive, Mauritius, Indian Ocean
2. Department of Anatomy, Bharati Vidyapeeth Medical College, Pune, India

E-mail of Corresponding Author: drmadhavmutalik@yahoo.com

ABSTRACT

Tinospora cordifolia (*Gulvel)* is traditionally used in ayurvedic medicine for apparently much varied conditions. It is commonly used in combination with other substances or sometimes alone. Supportive evidences from pharmacological studies suggest its prominent role in immune-modulation in conditions like diabetes mellitus, obstructive jaundice, and hepatic and splenic injury. Antioxidant, radioprotective, antihyperglycemic, antiinflammatory, antiulcer, and antispasmodic properties, and capacity to dissolve urinary calculi also have supportive evidences. It is a potential antidepressant and enhances cognition and memory. Immune-modulation, preventing oxidative damage, and relieving inflammation are likely explanations for benefits in infections, joint inflammation, and allergies. The constellation of various activities plays a role in its protective effects against antitubercular and cytotoxic drugs, and toxins. It is helpful in potentiating other substances in the form of "Shodhan-Vidhi". This review discusses details of its formulations, the relevance of supportive evidences and possible mechanisms of actions for its claimed benefits, and future prospects. It shows the links between "what is believed" and "what is known" regarding use of *Tinospora cordifolia*.

Keywords: Claims and evidences, *Gulvel*, mechanism of action, plant, *Tinospora cordifolia*, "Shodhan-Vidhi"

INTRODUCTION

Tinospora cordifolia [*Tinospora cordifolia* (Willd.) Miers ex Hook. F. & Thoms], known as *Gulvel* or *Guduchi*, has been an extensively used and investigated plant from family Menispermaceae for its varied activities. It is a deciduous, fleshy, robust climber growing with support of mango or neem trees, and is also known as *Cocculus cordifolius* Dec, *Menispermum cordifolium* Willd., and *Tinospora glabra* (N. Brum.) Merr[1]. "Giloya", the Hindi name of the plant refers in Hindu mythology to a heavenly elixir used to stay off the aging and to stay young forever. The Sanskrit name "Guduchi" means one that protects from illnesses. Hence the words "rejuvenator" or "adaptogen" seem to have appeared in literature[2]. It is found in India, China, Myanmar, Sri Lanka, Thailand, Philippines, Indonesia, Malaysia, Borneo, Vietnam, Bangladesh, North Africa, West Africa, and South Africa. In India, it is abundantly found in Maharashtra, Gujarat, Madhya Pradesh, Himachal Pradesh, and some other states in North and South

India[3,4,5,6]. In crude form, it is available in market mostly as dried stem pieces. The present review discusses its formulations and methods of use, and searches the correlation of its traditional or claimed uses with possible mechanisms of action in light of evidences from modern pharmacologic studies, and shows the link between "the believed" and "the known". Throughout the present article, the plant is referred to as *Gulvel* or *Tinospora cordifolia* or *Tinospora*.

Names and ayurvedic pharmacodynamics

Its various names include: Gulvel, Giloe (English); Foon kan thang (Malaya); Makabuhay (Philippines); Brotowali, Andawali, Putrawali, Daun gade (Indonesia); and Boraphet, Wan kab hoi yai (Thailand)[7,8]. Some names in Indian languages are: Amrita, Amritvalli, Madhuparni, Giloe, Guduchi, Kundalini (Sanskrit); Giloya, Guduchi (Hindi); Ambarvel, Gharol, Gulvel (Marathi); Nimgilo, Gulancha, Palo (Bengali); Jivantik, Tippaatige (Telugu); Shindilakodi (Tamil); Ambrithu, Chittamrutu (Malayalam); Gilo, Batindu, Garham, Ga (Punjabi); Galo, Galonovelo (Gujarati); Ambritaballi, Uganiballi (Kannada); Amarlata, Siddhilata (Assamese); Amrita, Gilo (Kashmiri); Gulancha, Gurcha (Kumaon); Harajora, Harajuri, Harjora (Mundari); Guluchi, Gulochi (Oriya)[1,7].

Gulvel is an ayurvedic drug as per the Drugs and Cosmetic Act of India (1940). Its stem, leaves, fruits, and seeds have been mentioned to be useful; however, maximum activities are ascribed to its stem. Its taste is bitter, pungent, and astringent[3]. Ayurvedic pharmacodynamic properties for "Rasa" are "Tikta" (bitter) and "Kashaya" (astringent); for "Guna" are "Laghu" and "Snigdha" (light and oily); for "Virya", it is "Ushna" (hot); and for "Vipaka", it is "Madhura" (sweet). It has been called "Tridosha-Shamak"; means useful for alleviating all three "doshas" ("Kafa", "Vata", and "Pitta")[6].

Market formulations, dosages, and mentioned indications

Gulvel is available as tablets and syrups. Ayurvedic formulations like Amritarishta, Amrtottara kvatha churna, Guduci taila, Guduchyadi churna, Guduchyadi-kwatha, Guduchi sattva, and Chinnodbhavadi kvatha churna have *Gulvel* as one of the constituents[1]. Some examples of strength and/or dosage and the mentioned indications include: 37.5 mg (for general debility, fatigue, old age, and as immunostimulant), 50 mg (antacid), 250 mg (menstrual disorders) in a combination[9]; 600 mg tablet twice daily (recurrent infections, to increase phagocytosis, antiinflammatory, neutralizing toxins, chronic ear-nose-throat infections, stimulating growth of epithelial cells)[10]; 50 mg tablet twice daily in a combination (hematinic, hepatoprotective, bone marrow stimulant, antioxidant, and for alleviating degenerative processes in diabetes)[10]; 4, 20, 500 mg tablets (immune-modulator in infections, tuberculosis, malaria, diabetes, and used with antimicrobials and nonsteroidal antiinflammatory drugs)[10]; 200 mg tablet twice daily in a combination (rheumatoid arthritis)[10]; 300 mg tablet twice daily (hematinic, immune-modulator in chronic fever and infectious diseases)[10]; 3-6 g (as powder) and 20-30 g (for decoction) as per Indian Herbal Pharmacopoeia[11]; 68.96 mg in a combination making a 500 mg tablet and 2 tablets twice daily as Diabetes care tablet[12]; and 49 mg in combination making a 100 mg tablet, advised as 1 tablet twice daily for chronic recurrent ear-nose-throat infections[13].

Some tribals who have been using *Gulvel* are: Garo tribals from Bangladesh for chicken pox, rheumatism, and helminthiasis[5]; and those from India are, Korkus (Melghat, Maharashtra) for polyuria, diabetes, and fever[14], Gond tribals (Kukrakhappa, Madhya Pradesh) for typhoid fever, malaria[15], Tagin tribals (Arunachal Pradesh) for scabies and skin diseases[16], and Baiga tribals (Varanasi district, Uttar Pradesh) for fever[17].

Constituents and nutritive values

Tinosporine, Tinosporaside, cordifolide, cordifol, and hepatacosanol are important constituents of *Gulvel*[18]. Barberine and palmatine are major alkaloids in stem. The glucosides are 18-norclerodane glucoside, sesquiterpenes like tinocordioside, tinocordifolioside, tinocordifolin, tinosponone, and cordioside, cordifolisides, and syringene[1,3]. The stem contains immunologically active substances – arabinogalactan and (1,4)-alpha-D-glucan[19,20].

Crude values for food content in *Gulvel* include high fibre (15.9%), sufficient protein (4.5%-11.2%), sufficient carbohydrate (61.66%), and low fat (3.1%)[21,22]. Nutritive value is 292.54 calories per 100 g[21,23]. *Gulvel* has high potassium (0.845%) (Regulatory function of nerve impulse)[21,24], high chromium (0.006%) (Regulation of carbohydrate utilization and pathophysiological alternations in diabetes mellitus)[25,26], sufficient iron (0.28%) (Hematopoietic functions)[21,27,28], and sufficient calcium (0.131%) (Regulatory functions in blood coagulation, and nervous, cardiovascular, and musculoskeletal systems[21,29,30].

Claimed or traditional uses

These include general debility, fatigue, old age, hematinic, adaptogen, rejuvenator, and tonic, and bleeding piles[1]; bleeding and menstrual disorders like metrorrhagia, menorrhagia[9], postpartum hemorrhage[31], and as bone marrow stimulant[1]. Immune-modulation related claims include increasing phagocytosis, neutralizing toxins, stimulating growth of epithelial cells, and supposed beneficial effects in recurrent infections, chronic fever, tuberculosis, malaria, diabetes, chronic ear-nose-throat infections, and as adjuvant with antimicrobials or nonsteroidal antiinflammatory drugs[10,13], and to relieve itching[1]. Genitourinary conditions include "Mutrakriccha" (urinary trouble) - used alone or in combinations; and spermatorrhea, phosphaturia, dysuria, gonorrhea, chronic cystitis, treatment and prevention of urinary calculi, incontinence of urine, to decrease the elevated blood urea concentration[32], diuretic[33], and to treat impotence[31]. Inflammation, pain, and fever-related claims include rheumatoid arthritis and gout[3,10], and pain[33] and fever[1,31]. Uses for antioxidant effect include alleviating degenerative processes in diabetes[10], and for free radical-mediated injury, liver damage, jaundice, stress, and cancer[33]. Gastrointestinal claims include use as antacid, carminative (dyspepsia, nausea)[1,31,34], and protective[33]. Hypoglycemic properties (apart from immune-modulation and antioxidant properties) relate to its supposed use in diabetes[1,33]. Claims include antimicrobial and antihelminthic uses[1]. *Gulvel* has been claimed to be useful as a medium of "Shodhan-Vidhi"[35,36] (to increase effect of other substances like *Guggul*). Claims include erysipelas, ulcers, leprosy, snake bite, and scorpion bite[18,37,38,39].

Evidences and mechanisms of action

Immune-modulation:

Immune-modulation by *Gulvel* has been established in obstructive jaundice, tuberculosis, and cancer in human and animal studies[40,41,42,43,44,45,46,47,48]. Syringin

and cordial, isolated from *Gulvel* showed inhibition of C3-convertase in classic complement pathway, enhancement of humoral and cell-mediated immunity, increased IgG antibodies, and increase in granulocyte-macrophage colony-forming units. Macrophage activation by cordioside, cordiofolioside, and cordiol isolated from *Gulvel*, led to leucocytosis and enhanced neutrophil function[49]. Protective effects of *Gulvel* in Escherichia coli-induced peritonitis in mice showed improved phagocytic capacities of neutrophils. Cholestasis-induced immunosuppression in rats was significantly improved by *Gulvel*, suggesting its role as immune-modulator in obstructive jaundice[46,50]. Immunologically active substances, arabinogalactan[19], and the novel (1,4)-alpha-D-glucan derived from *Gulvel* were shown to activate immune system through macrophage activation via toll-like receptor-6 (TLR6) signaling, nuclear factor kappa B (NF-kappa-B) translocation, and cytokine production[20,51]. Antiangiogenic activity was shown through elevation of interleukin-2 (IL-2) and tissue inhibitor of metalloprotease-1 (TIMP-1)[52].

Immune-modulatory effects have implications in liver damage due to tuberculosis and anti-tuberculosis drugs, cancers and anticancer drugs, and malaria. Immune-modulation is also a likely basis for its claimed use as bone marrow stimulant, hematinic, tonic or rejuvenator, and the supposed beneficial effects in general debility and old age[1], due to additional antioxidant property. Supposed uses for prevention and management of recurrent infections including ear-nose-throat infections and symptomatic treatment of pruritus[10] also are related to immune-modulation.

Hepatoprotective functions:

Gulvel was shown to be protective against liver damage induced by carbon tetrachloride[53], antitubercular drugs[42,43], bile salts[54], in obstructive jaundice[44,46], and gamma radiation[55]. In vitro inactivation of hepatitis B and E surface antigens[56], and modifying Kupffer cell activity was demonstrated[45]. Protective effects extended to improvement in splenomegaly during chloroquine treatment of malaria[57].

Immune-modulation seems to have major contribution in hepatoprotective and splenoprotective activity of *Gulvel*[40,41,42,43,44,45,46,53,54,55,56].

Radioprotection was shown by recovery in spleen weight, decrease in apoptosis and DNA fragmentation, increase in splenocyte number, macrophage adherence, interleukin-1 (IL-1) beta, and granulocyte-macrophage colony-stimulating factor (GM-CSF)[55].

Antioxidant effects:

Phenolic compounds in *Gulvel* are antioxidants[58,59]. In vitro models showed nitric oxide and superoxide radical scavenging, inhibition of lipid peroxidation, reduction of ferric ions, and total antioxidant capacity[4]. It reduced superoxide and hydroxyl radical generation and the toxicity induced by free radicals. Alleviation of toxic effects of cyclophosphamide in mice was evident by total white blood cell counts, bone marrow cellularity, and esterase-positive cells. It partially reduced elevated lipid peroxides in serum and liver, and serum alkaline phosphatase and serum glutamic-pyruvic transaminase(SGPT)[60,61]. Its role in preventing oxidative stress associated with infections was suggested with reference to catalase, glutathione-s-transferase, glutathione peroxidase, glutathione reductase, superoxide dismutase, and polyphenoloxidase[62]. These effects (along

with immune-modulation) partially justify claims of benefit in general debility, fatigue, old age, and as hematinic, rejuvenator, tonic, and effects in chronic recurrent infections[58,59].

Cancer:

Anticancer actions of a formulation containing *Tinospora cordifolia, Asparagus racemasus, Withania somnifera,* and *Picrorrhiza kurrooa* were shown in mouse macrophages[63,64]. Effects related to modulation of chemotaxis, interlukin-1 (IL-1), and tumor necrosis factor in ochratoxin-treated macrophages. Aqueous, methanolic, and dichloromethane extracts of *Gulvel* showed dose-dependent increases in lethality to HeLa cells (maximum activity with dichloromethane extract)[65]. Effects were related mainly to immune-modulatory functions. Antioxidant property also correlates with amelioration of cyclophosphamide toxicity[60,61].

Diabetes mellitus:

Hypoglycemic activity of *Gulvel* was shown in alloxan-diabetic rats[66]. The aqueous and alcoholic extracts reduced fasting blood sugar and improved glucose tolerance followed by deterioration after one-month treatment. Significant hypoglycemic effects were shown in rabbits treated with aqueous, alcoholic, and chloroform extracts of *Gulvel* leaves. Aqueous root extract of *Gulvel* caused a significant reduction in blood glucose, brain lipids, and hepatic glucose-6-phosphatase, serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase, and increased the body weight, hemoglobin, and hepatic hexokinase levels[1,67]. An indirect action of *Gulvel* on carbohydrate metabolism was suggested through its favorable effect on endogenous insulin secretion and glucose uptake, and inhibition of peripheral glucose release[68,69]. Amelioration of experimental diabetic neuropathy and gastropathy in rats and modulation of morphology and some gluconeogenic enzymes in diabetic rat kidney suggest potential for preventing the complications of diabetes[70,71].

Inflammation, pain, and fever:

Extensive animal studies with aqueous and alcoholic extracts of *Gulvel* in acute and subacute inflammation using models of carrageenin-induced hind paw edema, induced edema and arthritis, adjuvant-induced arthritis, cotton pellet granuloma, and formalin-induced arthritis, and a clinical trial in rheumatoid arthritis showed its antiinflammatory action[72,73,74,75,76]. Effect comparable to indomethacin was demonstrated and mechanism of action similar to nonsteroidal antiinflammatory drugs was suggested[73,74,75,77].

Significant peripheral analgesic activity of *Gulvel* was shown by Randall-Selitto assay in rats and acetic acid-induced writhing test in mice. Although potentiation of morphine analgesia was demonstrated, central analgesic effect was not observed on tail clip and hot plate tests in mice[1,31,78,79,80,81,82].

Antipyretic activity of ethanolic extract, hexane soluble preparation, and chloroform soluble portions *Gulvel* stem showed antipyretic activity on experimental evaluation in rats[31,78,79,80,81].

These studies support antiinflammatory activity of *Gulvel*, relating to its mechanism of action similar to nonsteroidal antiinflammatory drugs[76,77]. Since central analgesia was not demonstrated, the suggested analgesic uses of *Gulvel* seem to correlate with peripheral analgesic activity to relieve the pain associated with inflammation[75]. This evidence supports the claimed uses in rheumatoid arthritis and gout[32].

Depressive disorders, stress, cognition, and memory:

Traditional claims of antistress activity of *Gulvel* have supportive evidence of normalization of stress-induced biochemical changes in norepinephrine, dopamine, and 5-hydroxytryptamine in experimental rat models and improved levels of 5-hydroxyindoleacetic acid (5-HIAA) (a metabolite of 5-hydroxytryptamine) in mice with ethanolic roots extracts[83,84,85]. Depression is characterized by decreased brain levels of monoamines like norepinephrine, serotonin, and dopamine. Established antidepressants act by inhibiting reuptake or breakdown of these amines and increasing their levels at postsynaptic receptors. Antidepressant-like effect *Gulvel* was significantly reversed on tail suppression test by pretreatment of animals with prazosin (an alpha-1 adrenoceptor antagonist), sulpiride (a selective dopamine D2-receptor antagonist), p-chlorophenylalanine (PCPA - a serotonin synthesis inhibitor), and baclofen (GABA-B agonist). Inhibition of metabolism of monoamines, particularly serotonin and noradrenaline was also demonstrated[86]. Hence the mechanism of antistress and antidepressant activities of *Gulvel* relates to interaction with alpha-1 adrenergic, dopaminergic (D2), serotonergic, and GABA-B receptors leading to increased levels of norepinephrine, dopamine, serotonin, and gamma-aminobutyric acid (GABA)[86]. Potentiation of brain monoamines by inhibition of monoamine oxidase is another suggested mechanism[86]. GABA-B receptor antagonism is suggested as a basis for development of novel antidepressants[87]. Barberine, an alkaloid in *Gulvel* has been reported to have antidepressant effect[88], and hence barberine seems to be an active component playing role in antidepressant effect of *Gulvel*.

Gulvel is mentioned as a "medhya rasayana" (learning and memory enhancer) and for "bhrama" (vertigo) in Ayurveda[89]. Significant response to *Gulvel* was reported in children with moderate degree of behavioral disorders and mental deficit, with improvement in intelligence quotient levels[89]. In a 21-day randomized double-blind placebo-controlled study, pure aqueous root extract enhanced verbal learning and logical memory[90]. *Gulvel* was shown to enhance cognition and memory in normal rats and to reverse cyclosporine-induced memory deficit. Alcoholic and aqueous extracts produced decrease in learning scores in Hebb-William maze and retention memory, with protection of hippocampal neurodegenerative changes on histopathological examination in cyclosporine-treated rats[91].

***Gulvel* as a medium of "Shodhan-Vidhi":**

"Shodhan-Vidhi" relates to combining a substance with another substance to increase its activity and to help counter some of its unwanted effects[36]. Modern pharmacological studies to explore "Shodhan-Vidhi" include its effect with another substance called *Guggul* (*Commiphora wightii*) for antispasmodic activity, which was demonstrated in guinea pig ileum. It indicated muscarinic blockade, histaminergic blockade or possibly phosphodiesterase inhibition or inactivation of calcium channels[35]. *Gulvel* enhanced the activity of *Guggul*. When Guggul was used alone, the effect of *Guggul* was significantly less[36]. Use of *Gulvel* combinations has a potential basis for clinically desirable drug interactions[92].

Diarrhea, dysentery, peptic ulcer, abdominal pain, and gastrointestinal protection:

The claimed use in non-specific diarrhea is supported by evidence from pharmacological studies in guinea pig

ileum, when *Gulvel* was used with *Guggul* (mentioned earlier)[35,36]. Antispasmodic activity was demonstrated against spasm induced by acetylcholine, histamine, and barium chloride[35,36], supporting the claimed use[14] as gastrointestinal protective in nonspecific diarrhea. Smooth muscle relaxing action could be further explored for uterine muscle for confirmation of supposed usefulness in dysmenorrhea.

A formulation containing *Tinospora* showed increase in gastric fluid pH and reduced ulcer index and total acidity in rats in pylorus-ligation and ethanol-induced gastric mucosal injury models[93]. *Gulvel* ethanolic root extract in combination with *Centella asiatica* afforded significant protection against restraint stress-induced ulcer formation, an activity comparable to diazepam in rats[94]. Histaminergic (H2 receptor) blockade and muscarinic blockade[35] are likely mechanisms for antiulcer activity and for claimed antacid or carminative uses[2,31]. The same mechanism can explain symptomatic relief in dyspepsia, belching, bloating, flatulence or stomach pain relating to term "Ajirna" or "Agnimandhya" in literature[34].

Genitourinary system and reproductive system:

Experimental evaluation showed benefits of *Tinospora* for dissolving urinary calculi[95]. In rats and in human volunteers, it had diuretic effect comparable to hydrochlorothiazide[96]. Decreased weight of testes, epididymis, seminal vesicles, and ventral prostate was demonstrated in male rats, a potential for antifertility activity[97].

Uses for dissolving urinary calculi, as a diuretic, and for decreasing blood urea concentration in uremia are thus substantiated[95,96,98]. Benefit in urinary tract infections does not have evidence of direct antibacterial action, and is likely to have a correlation with its antiinflammatory and immune-modulating activities. Supposed use to treat impotence does not correlate with apparently opposite finding of antifertility action seen in male rats[31,97].

Infections:

Gulvel is claimed to be useful in various infective conditions[1,10,13,78,79,80], and tuberculosis[7,10,22,81]. It has no specific antibacterial activity against E. coli, Salmonella typhi, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa or Proteus vulgaris[14,50]. There seems to be insufficient evidence for its direct antimicrobial activity. Mechanism that plays a role in infections is the protective effect by immune-modulation including effects on polymorphonuclear cells, phagocytes, and on macrophage function[46,49,50]. Another mechanism involves its antioxidant property, which is beneficial in decreasing oxidative stress and damage related to infections[61]. Use in infective diarrhea does not seem to involve antibacterial properties against any of the common enteric pathogens (Salmonella, Escherichia coli, Shigella, Proteus or Pseudomonas), but more of antispasmodic effect[14,35,36]. Benefits in urinary tract infections do not have supportive evidence of direct antimicrobial activity, and may be related to pain relief by dissolving urinary calculi, alkalinization of urine, and immune-modulation[95,96,98]. Similarly, there is no sufficient evidence of direct antimicrobial activity in tuberculosis; however, its use in tuberculosis relates to immune-modulation[40], and preventing hepatotoxicity of antitubercular drugs[42,43]. Claims for usefulness in viral infections do not have supportive evidence from pharmacologic studies. There was evidence of clinical and symptomatic benefits in fungal otitis externa, chronic sinusitis, chronic tonsillitis, and chronic suppurative

otitis media[13]. In absence of proven antimicrobial activity; immune-modulation, and antioxidant and antiinflammatory action is the likely mechanism involved.

Skin disorders and leprosy:

Traditional use of *Gulvel* has been mentioned in skin diseases[38,39]. In Ayurveda, it has been mentioned as "Kushtahara" (means, useful in leprosy), and useful in skin disorders like "Kandu" and "Visarpa"[99]. *Gulvel* has been shown to have beneficial antileprotic activity in a combination formulation[99].

Bronchial asthma:

Gulvel stem aqueous extract decreased bronchospasm in guinea pigs, capillary permeability in mice, and reduced number of disrupted mast cells in rats[100,101]. Immune-modulation is also likely to be a responsible mechanism in allergies and bronchial asthma.

Snake bite and scorpion bite:

Use has been mentioned in snake bite and scorpion bite due to its ability to remove exogenous and endogenous toxins[18,37]. The most likely mechanism relates to immune-modulation and antioxidant properties.

Osteoprotection:

Slower bone loss in tibia than that in controls was demonstrated in rats treated with *Gulvel*, showing potential for osteoprotective activity. Serum osteocalcin and cross-laps levels were significantly reduced. This suggested its potential use as an anti-osteoporotic agent[102].

Seizures and convulsions:

In comparison with phenytoin, ethanolic extract of *Gulvel* showed 61.1 percent inhibition of electroshock seizures in rats[103]. Another report shows lack of significant anticonvulsant activity during maximum electroshock and chemoshock tests in mice[1].

Link between claims and evidences: the believed and the known

Evidences from various pharmacological studies suggest many overlapping mechanisms of actions likely to be contributing to beneficial effects of *Tinospora cordifolia (Gulvel)*. Immune-modulation, protective actions, and antioxidant properties seem to contribute profoundly in diabetes, obstructive jaundice, malaria, hepatic and splenic injury, protection from allergens and toxins, infections, inflammation, rheumatoid arthritis, gout, leprosy, and in preventing adverse effects of anticancer and antituberculosis agents[41,42,44,46,57,60,61,64,65]. Role of its antioxidant properties[60,62] in degenerative diseases can serve as a potential area for further work.

In addition to immune-modulation and hypoglycemic activity, high chromium content, and protective effects in preventing complications of diabetes (neuropathy, nephropathy, and gastropathy) are remarkable[66,67,68,70,71]. Exploring these areas and search for possibility of its insulin sensitizing and/or insulin secretogogue effect will help to further establish its status in management of diabetes.

Antidepressant effects of *Gulvel* by various different mechanisms directed towards concentrating and potentiating brain amines (norepinephrine, dopamine, and serotonin) has been a novel remarkable finding. Increased amine levels in brain as well as preventing breakdown of amines by inhibiting monoamine oxidase were the two important evidences[86,87,88]. Monoamine oxidase inhibitors were the older and comparatively more toxic antidepressants, whereas the selective serotonin reuptake inhibitors (SSRI) are the antidepressants of modern era with fewer adverse effects[104]. Since *Gulvel* has not been mentioned to be a highly toxic substance, it will be relevant

to search if it has effects similar to the SSRI. Antistress activity and improved learning and memory are potential directions for further research[83,84,90,91].

Tinospora is shown to have antiinflammatory effect similar to nonsteroidal antiinflammatory drugs, justifying its benefits in rheumatoid arthritis and gout[74,75,77]; however, there is no evidence of specific activity directed against uric acid synthesis or excretion. Benefits are related to relief of inflammation and associated pain, and immune-modulation. It is remarkable that despite having a mechanism like nonsteroidal antiinflammatory drugs (NSAIDs), it has antiulcer activity[93,94]. This finding may provide *Gulvel* a status better than traditional NSAIDs (which precipitate peptic ulcer). There is a potential for further work to search if it has any specific properties like celecoxib, of selectively inhibiting cyclooxygenase-2 (COX-2) enzyme secreted at sites of inflammation (without inhibiting COX-1 in the stomach)[105]. This shall help to clarify the gastric mucosal protection offered by *Gulvel*. In addition, its antispasmodic action is thought to involve possible histamine receptor (H_2) blockade and muscarinic blockade. It will be interesting to explore if it provides protection against peptic ulcer by similar mechanisms. Obviously, a potential exists for verifying its status in treatment of peptic ulcer.

There is no evidence for direct antimicrobial activity of *Gulvel*[14,49,50]. Immune-modulation, protective action against allergens and toxins, and preventing oxidative stress related to infections work as contributory mechanisms for beneficial effects in infections. These conditions include acute or chronic and recurrent infections of respiratory, urinary, and gastrointestinal tracts. Dissolving urinary calculi serves as an additional mechanism in related urinary infections and dysuria[95]. There is a potential scope for further establishing the claimed and observed beneficial effects in decreasing blood urea level.

Gulvel is used in combination with other agents in ayurvedic formulations, and has a rationale of "Shodhan-Vidhi" described elsewhere in this article, and has supportive evidence from a modern pharmacologic study pertaining to its antispasmodic activity[35,36]. There is scope for establishing such evidence for its benefit with other substances and for other effects. There is also potential scope for searching the mechanisms of beneficial drug interactions when *Gulvel* is used in combination formulations. A parallel principle in pharmacology involves a type of drug interaction when a substance helps to counter the unwanted effects of another substance present in combination, described as reparative drug interaction under some clinically desirable drug interactions[92]. Exploring possibility of specific additive or synergistic effects of *Gulvel* with other substances and the pharmacokinetic and pharmacodynamics of such combinations will help to establish rationale behind combination formulations of *Gulvel*.

Exploring "Shodhan-Vidhi" has established its antispasmodic effect. In addition, it was shown to prevent brochospasm in animals[100,101]. Hence the smooth muscle relaxation involving H_2 receptor blockade and muscarinic blockade can be explored further for its potential for relaxing brochial and uterine muscle.

Since *Gulvel* has been shown to have different diverse effects, deciding on its selectivity of action at particular dosages, detailed pharmacodynamic and pharmacokinetic profile, dose ranges for

various actions, and safety profile are some more potential areas of research.

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