International Journal of Innovation Scientific Research and Review
Vol. 04, Issue, 02, pp.2411-2415, February 2022
Available online at http://www.journalijisr.com
SJIF Impact Factor 4.95

IJISRR

ISSN: 2582-6131

Research Article

METFORMIN: A NOVEL ANTIDIABETIC DRUG OF BOTANICAL ORIGIN

[1,] * Ravindra B. Malabadi, [2]Kiran P. Kolkar, [3]Manohara Acharya, [1]Raju K. Chalannavar

[1]Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India.
[1]Miller Blvd, NW, Edmonton, Alberta, Canada.
[2] Department of Botany, Karnatak Science College, Dharwad-580003, Karnataka State, India.
[3]Department of Applied Botany, Mangalore University, Mangalagangotri, Mangaluru-574199, Karnataka, India
[3]Department of Botany, Canara College, Mangaluru-575003, Karnataka, India.

Received 24th December 2021; Accepted 26th January 2022; Published online 28th February 2022

ABSTRACT

Many of the currently available drugs in the market have been directly or indirectly derived from plants and one of the best example is metformin synthesized in 1922 from the noxious weed, Galega officinalis. Metformin (1-1-Dimethyl-biguanide) (C4H11N5) is a synthetic biguanide orally effective and insulin sensitizing anti-diabetic drug. The hypoglycaemic drug metformin is derived from Galegine, which is found naturally in Goat's rue (Gallega officinalis). The common names of Galega officinalis include Goat's Rue, French lilac, Spanish sanfoin, False indigo, Professor weed and Italian fitch. Biguanides such as metformin are widely used worldwide for the treatment of type-2 diabetes. The identification of guanidine and related compounds in French lilac plant (Galega officinalis L.) led to the development of biguanides. Therefore, natural source of galegine, which is a precursor of metformin is widely used as an oral antidiabetic agent. French lilac (Gallega officinais) is rich in guanidine, a substance with blood glucose-lowering (hypoglycaemic) activity that is present in the basic structure of metformin.

Keywords: Antidiabetic drug, Gallega officinalis, herbal medicine, metformin noxious weed.

INTRODUCTION

Metformin (1-1-Dimethyl-biguanide) (**$C_4H_{11}N_5$**) is commonly referred as the *Glyciphage* (Glucose destroyer) which has been known for centuries as a herbal medicine in the treatment of an inflammatory disorder, type-2-diabetes mellitus (1-10). Metformin (1-1-Dimethyl-biguanide) (**$C_4H_{11}N_5$**) is a synthetic biguanide, orally effective and insulin sensitizing anti-diabetic drug, which for the most patients is the first line anti-hyperglycemic treatment for the type 2 diabetes mellitus (1-16). Metformin was first synthesized in 1922 and its development was based on knowledge from folk medicine that the active, but toxic, constituent from *Galega officinalis* (French lilac) that could treat 'sweet urine' was the guanidine, galegine (1-20, 28, 29). Galegine, a guanidine derivative, has been shown to be synthesised in the seedlings, leaves, flowers, and fruits of *Galega officinalis* (1-22). Currently, there are numerous antidiabetic agents available for the treatment of diabetes mellitus (DM), which target different receptors (13-27). The most important classes of antidiabetic oral medicines include biguanides, such as metformin, sulfonylureas, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 inhibitors, sodium glucose cotransporter (SGLT2) inhibitors and α-glucosidase inhibitors (10-28).

Metformin is beneficial in reducing cholesterol not only in diabetic patients but non-diabetics as well. Metformin does not cause hypoglycemia by itself, but when used in combination with other diabetic treatments, there is a potential for hypoglycemia (1-25). Hypoglycemia can be avoided by careful monitoring of blood glucose levels. Metformin is an affordable option due its simple synthesis and cost effectiveness. Metformin remains one of the best anti-diabetic drugs on the market because of its efficiency in lowering the blood glucose levels in patients with type 2 diabetes and its extremely low risk of side effects such as hypoglycemia and acidosis (1-27).

***Corresponding Author: Ravindra B. Malabadi,**
1Department of Applied Botany, Mangalore University, Mangalagangotri-574199, Mangalore, Karnataka State, India. 1Miller Blvd, NW, Edmonton, Alberta, Canada.

Metformin has also been shown to decrease cholesterol levels, reduce weight, and prevent death due to cardiovascular disease. The flowering aerial parts of *Galega officinalis* were used in the past to alleviate the polyuria associated with long-term hyperglycemia, but also used in the treatment of many other conditions from tuberculosis, ubonic plague, and malignant fevers to epilepsy, helminthiasis, and various infectious diseases (1-28).

Metformin Hydrochloride (Glyciphage) is a member of the biguanide class of drugs and used in the treatment of a number of diseases and conditions, of which type 2 diabetes is most prevalent (1-29). Type 2 diabetes is characterized by abnormally high levels of glucose in the blood due to either insulin resistance of the cells or too much glucose production in the liver or a combination of both. The main concerns with any available treatment for diabetes include hypoglycemia and diabetic ketoacidosis (1-20). Diabetic ketoacidosis (DKA) as a result of prolonged elevation of glucose in the blood is a very serious state. It includes severe dehydration from a combination of loss of electrolytes, sweating, hyperventilation, and fever, as well as includes cardiac and skeletal muscle toxicity. Diabetic ketoacidosis (DKA) can be easily avoided with the close monitoring of blood glucose levels (1-27).

Metformin's mechanism of action is related to increasing the activity of energy sensor adenosine-monophosphate-activated protein kinases, which increases glucose uptake in various tissues, increases lipid metabolism, and decreases glucose production in the liver (10-29). Thus metformin lowers blood glucose concentrations but also increasingly seems to produce a host of other beneficial effects in both diabetics and non-diabetics. Metformin is a substituted biguanide synthesized from the guanidine active principle (1-18). Metformin's official chemical name is N, N-dimethylimidodicarbonimidic diamide (also called 1,1-dimethylbiguanide), and its formula is **$C_4H_{11}N_5$**. Therefore, research work on galegine and its derivatives (guanidines and biguanides) was considered as a milestone in the development of oral antidiabetic pharmacotherapy (1-28).

DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disease with life threatening complications (12-18, 34, 35). There are two types one is Type-1 Diabetes and it is insulin dependent. Another second one is Type-2 Diabetes which is non-insulin dependent. Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post increased blood sugar levels (34, 35). Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin. On the other hand patients suffering from Type II diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and medication(1-20, 34, 35). The β-cells in the pancreas are the key players in glycemic homeostasis. Pancreatic β-cells are the only endocrine cells known to produce insulin. Insulin is a protein hormone that regulates the metabolism of glucose, fat, and protein in the body. Any defect in insulin production and action leads to serious metabolic problems (1-8, 34, 35). Type II diabetes is the more common form of diabetes constituting 90% of the diabetic population (1-20, 34). Symptoms for both diabetic conditions may include: (a) high levels of sugar in the blood; (b) unusual thirst; (c) frequent urination; (d) extreme hunger and loss of weight; (e) blurred vision; (f) nausea and vomiting; (g) extreme weakness and tiredness; (h) irritability, mood changes etc (1-20, 34, 35).

METFORMIN: BOTANICAL ORIGIN

Its botanical history can be traced back to the use of *Galega officinalis* (*Leguminosae*) Linn as a herbal medicine native to Europe (France, Spain, Italy, UK) and Western Asia (1-28). The plant was introduced into North America in 1891 and is now classed as a noxious weed in many states of the USA (20-31). The biguanide metformin was isolated from the flowers of the plant *Galega officinalis* (goat's rue or French lilac), and has been used as a herbal treatment for the symptoms of diabetes mellitus (1-27). *Galega officinalis* is a toxic plant due to the alkaloid galegine (1-27). In Europe, wild *Galega officinalis* was widely recognised as an animal galactagogue from which it gained its name ('Galega' being derived from the Greek for 'milk stimulant') (1-28). The hypoglycaemic drug metformin is derived from Galegine, which is found naturally in Goat's rue (*Gallega officinalis*). Therefore, natural source of galegine, which is a precursor of metformin, now a very widely used as oral antidiabetic agent (1-25). The botanical weed plant, *Galega officinalis,* was given to diabetic patients because it has relieved the excessive urination symptom (1-26). Metformin is in the class of biguanides and is currently a first-line treatment for the type-2-diabetes mellitus disorder (1-23). The plant *Galega officinali* was also given to patients during plague epidemics to promote perspiration. Further research showed that the active ingredient in French lilac that resulted in lowering of blood glucose was galegine, or isoamylene guanidine (1-27). Guanidine derivatives, including metformin, were synthesised and some (not metformin) were used to treat diabetes in the 1920s and 1930s but were discontinued due to toxicity and the increased availability of insulin (1-31). Metformin was rediscovered in the search for antimalarial agents in the 1940s and, during clinical tests, proved useful to treat influenza when it sometimes lowered blood glucose (1-29). This interesting research work was pursued by the French physician Jean Sterne, who first reported the use of metformin to treat diabetes in 1957 (1-28). However, metformin was considered weaker than other glucose-lowering biguanides and received limited use. When the other biguanides (phenformin and buformin) were withdrawn in the late 1970s because of links to lactic acidosis, metformin was spared, but mostly rejected (1-29).

The common names of *Galega officinalis* include Goat's Rue, French lilac, Spanish sanfoin, False indigo, Professor weed and Italian fitch (1-25). *Galega officinalis* was found to be rich in guanidine, a substance with blood glucose-lowering activity that formed the chemical basis of metformin (1-27). *Galega officinalis* (Leguminosae) is a perennial herb with white, blue or purple flowers that grows over three feet high and is found in the most temperate regions, including Britain (1-24). Aerial parts of the plant were used medicinally in medieval Europe to treat plague, worms, snake bites, miasma, dysuria and St Vitus dance, and the plant was fed to livestock to increase milk yield (1-29). Moreover, due to its presumed impact on increasing milk yield, galega was used as a galactagogue in humans (1-24). At the beginning of the 19th century, it was extensively cultivated as a forage crop in the United States, but in 1986 Keeler *et al.,* (25) reported the clinical symptoms of poisoning in sheep, occurring at doses of about 0.8g of dried *Galega officinalis* (25). Galegine became the basis for the synthesis of metformin (1,1-dimethylbiguanide), commonly used as a first-line drug for monotherapy and combination therapy to manage hyperglycemia in type -2-diabetes (1-27).

Galega officinalis, a noxious weed is considered as a tap rooted perennial, grows from 0.6 to 1.5 meters tall, and reproduces by seed (31). It has oddly-pinnate leaves with 6-12 pairs of leaflets (31). The plant bears most commonly purple, but also blue to white papilionaceous flowers in terminal and axillary racemes (31). The seed pods are roughly 2.5 cm long, narrow and round in cross section (31). Seeds are about 2.5 times the size of alfalfa seed, and yellowish in color, and can remain viable in the soil for at least 15 years (31). Seed coats have a physical dormancy, and must be scarified to allow water up take and germination (31). *Galega officinalis* is also involved to fix atmospheric nitrogen when it is associated with a bacterium in a symbiotic relationship (31). The bacteria strain, *Rhizobium galegae*, associated with Goatsrue is host specific and does not infect other legumes; and likewise goatsrue will not be associate with any other rhizobium (31). The *Galega rhizobium* is a fast growing rhizobium with an indeterminate root nodule, which is common among temperate legumes. Goatsrue has also become problematic in New Zealand, England, Chile, Ecuador, and Argentina (31). *Galega officinalis* (Goatsrue) is found in 10 states throughout the United States: Utah, Colorado, Washington, Nebraska, Maine, Massachusetts, New York, Pennsylvania, Connecticut, and Washington D.C (31). It is found on 13 state noxious weed lists and is also classified as a federal noxious weed (31).

METFORMIN: HISTORICAL BACKGROUND

Galega officinalis, a plant that contains biguanide, has been used since the middle ages for the treatment of diabetes (1-29). *Galega officinalis* was also used in folklore medicine to treat symptoms now ascribed to type 2 diabetes and some versions of Culpeper's herbal suggested that it has antidiabetic properties (1-20). Nicholas Culpeper's treatise was first published in the 17th century (1-23). There are more detailed accounts of extracts of *Galega officinalis* being used to treat diabetes in France up to the 1930s (1-28). Studies in the late 1800s indicated that *Galega officinalis* was rich in guanidine and in 1918 guanidine was shown to possess hypoglycaemic activity in animals (1-20). However, guanidine was too toxic for clinical use and attention turned to galegine (isoamylene guanidine), a less toxic extract of *Galega officinalis* that was used briefly as an antidiabetic agent in the 1920s (1-27). The latter prompted Jean Sterne to investigate the glucose-lowering activity of dimethylbiguanide. Jean Sterne (1909–1997) was a physician and clinical pharmacologist who trained in diabetology under Francis

Rathery at the Hôpital de la Pitie in Paris (1-20). It was here that Sterne first conducted studies with galegine (1-30). In 1956, Sterne selected dimethylbiguanide (metformin) for clinical development and proposed the name 'Glucophage' (glucose eater). Many biguanides and related guanidine derivatives have been examined as potential antidiabetic agents (1-27).

In 1922 guanidine was found to be the active ingredient in *Galega officinalis* that lowered blood glucose levels (1-28). The guanidine structure of metformin is a nitrogenous analog of carbonic acid, and includes two methyl groups, whereas phenformin and buformin have apparently toxic aromatic rings or alkyl chains (1-28). Phenformin and buformin were synthesized as part of the biguanide class in the 1950s, but were withdrawn in the 1970s because of increased incidences of death due to lactic acidosis and cardiac dysfunctions resulting from use of phenformin in treating those with type-2-diabetes mellitus disorder (1-26). Metformin has a greater association with reductions in weight and low-density lipoprotein (LDL) cholesterol, and a much lower risk of hypoglycemia when compared with sulfonylureas and with thiazolidinediones, a newer option in treating type-2-diabetes mellitus (1-28). Metformin carries a low risk of hypoglycemia because its primary action is inhibition of gluconeogenesis, the liver's production of glucose from non-carbohydrates such as proteins or fats (1-24). In contrast, the effect of the most other type-2-diabetes mellitus drugs is to stimulate insulin secretion (1-22). Metformin's beneficial effect on diabetes is dependent on there being circulating insulin in the blood (1-25). Thus it cannot be a substitute for insulin or the only treatment in insulin-dependent diabetes such as type-1-diabetes mellitus. Metformin is indicated in treating insulin-resistant classes of diabetes, such as type-2-diabetes mellitus or gestational diabetes (1-27).

PLANTS WITH BIGUANIDE RELATED COMPOUNDS (BRCS)

Furthermore, the corrected results of the Voges–Proskauer (V–P) assay (29) suggested that the highest amounts of biguanide related compounds (BRCs) were also present in green curry leaves (*Murraya koenigii* (L.) Sprengel) followed by fenugreek seeds (*Trigonella foenum-graecum* L.), green bitter gourd (*Momordica charantia* Descourt.), and potato (*Solanum tuberosum* L.) (29). Whereas, garlic (*Allium sativum* L.), and sweet potato (*Ipomea batatas* (L.) Lam.) contain negligible amounts of biguanide related compounds (BRCs) (29). Although, fenugreek, curry leaves, bitter gourd, garlic and sweet potato are known for antihyperglycaemic properties in Ayurvedic medicine for several centuries (9). The concept of synthesising biguanides, such as metformin, originated from the hypoglycaemic properties of plant guanidines (29). Biguanide related compounds (BRCs) were also quantified in fenugreek seeds, green curry leaves, green bitter gourd, garlic, sweet potato and potato tubers (29). The highest amount of biguanide related compounds (BRCs) was found in curry leaves followed by fenugreek, bitter gourd and potato (29). Garlic and sweet potato contained very low or negligible amounts of biguanide related compounds (BRCs) (29). If proper corrections for interfering compounds are employed, the V–P assay can be successfully used to quantify biguanide related compounds (BRCs) in plant species (29). BRCs in the plant food extracts were determined using the spectrophotometric method modified for 96-well microplates (29). This assay is based upon the reaction of the guanidine group with anaphthol- diacetyl at an alkaline pH (Voges–Proskauer or V–P reaction) (29). Free guanidines are widespread in plants. Biochemically, guanidine can serve as an immediate precursor for biguanide biosynthesis. The identification of BRCs and existence of the arginine–guanidine pathway in the plant species has also supported the proposed route of biguanide biosynthesis in the plant foods (29). Arginine can transfer its amidine group to a precursor of galegine by a transamidination reaction (29). A transamidination reaction could possibly occur between arginine and isopentenylamine (29). Similarly, galegine may serve as immediate precursor for biguanide biosynthesis in the plant (29).

Alkaloids, glycosides, saponines, gymnic acid, galactomannan, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, flavonoids, phenolics, amino acids and inorganic ions are a few of the plant-derived compounds that have demonstrated antidiabetic activity (29). Plant derived medicines have played a pivotal role in the health care (36-48). Many of these natural products have pharmacological or biological activity that can be exploited in pharmaceutical drug discovery and drug design (36- 48). Further, other medicinal plants used as antidiabetic agents are Insulin plant, *Costus speciosus* and *Gymnema sylvestris* (32-33). Rhizomes of *Costus speciosus* are the major source of diosgenin, curcumin and curcuminoids (32). Further *Gymnema sylvestris* is rich in the group of oleanane type triterpenoid saponins known as gymnemic acids and dammarenesaponins called gymnemasides (33).

METFORMIN: SIDE EFFECTS

Metformin (Glucophage or Glyciphage= Glucose eater) is not an insulin but is considered an insulin sensitizer (1-17). The dosage of metformin is usually 1-3 pills per day at different sizes of 500 mg, 850 mg, or 1000 mg, taken with meals in order to reduce adverse gastrointestinal side effects. Gastrointestinal effects occur in up to 50% of patients using metformin (1-22). Metformin could cause bloating, diarrhea, nausea, abdominal pain, vomiting, flatulence, anorexia, and dyspepsia, but these symptoms are almost always transient and resolved within a few days, especially when metformin is taken with food or in a gradual titration. Gastrointestinal effects are mainly related to metformin dosage which is usually changed or when taken in combination with other drugs (1-28). Gastrointestinal upset can cause severe discomfort and it is the most common when metformin is first administered, or when the dose is increased (1-30). Long-term use of metformin has been associated with increased homocysteine levels and malabsorption of vitaminB_{12}. High er doses and prolonged use of metformin are associated with increased incidence of vitamin B_{12} deficiency (1-24). The most serious potential adverse side effect of metformin is lactic acidosis (1-23). This complication is rare, and the vast majority of these cases seem to be related to conditions such as impaired liver or kidney function, rather than to the metformin itself. Metformin is not approved for use in those with severe kidney disease, but may still be used at lower doses in those with kidney problem (1-28). The most common symptoms following an overdose of metformin include vomiting, diarrhea, abdominal pain, tachycardia, drowsiness, and rarely, hypoglycemia or hyperglycemia (1-25).

METFORMIN: SYNTHESIS

Metformin was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of *N*,*N*-dimethylguanidine (1-24). In 1929, Slotta and Tschesche discovered its sugar-lowering action in rabbits, as the most potent biguanide analog (1-27). French diabetologist Jean Sterne studied the antihyperglycemic properties of galegine, an alkaloid isolated from *Galega officinalis*, which is related in structure to metformin, and confirmed as an antidiabetic before the synthalins were developed (1-24). Metformin hydrochloride (1,1-dimethylbiguanide hydrochloride) is freely soluble in water, slightly soluble in ethanol, but almost insoluble in acetone, ether, or chloroform. The

usual synthesis of metformin, originally described in 1922, involves the one-pot reaction of dimethylamine hydrochloride and 2-cyanoguanidine over heat (1-25). Metformin was first described in 1922 by Werner and Bell, and it involved a simple precipitation reaction of dimethylamine hydrochloride and 2-cyanoguanidine over heat (2-25). More reactions to produce metformin have been described and patented. Metformin hydrochloride, the salt version of the drug, is synthesized via the reaction of equimolar amounts of dimethylamine and 2-cyanoguanidine dissolved in toluene with cooling to make a concentrated solution, with equimolar amounts of hydrogen chloride slowly added. The mixture boils and then, after cooling, metformin hydrochloride is yielded in a precipitate with 96% yield (1-30).

Two synthetic diguanides, namely decamethylene diguanide (Synthalin A) and dodecamethylene diguanide (Synthalin B), were better tolerated and more effective, and these were used clinically in the 1920s (1-30). However, insulin was becoming more widely available and increased appreciation of the toxicity and limited efficacy of hypoglycaemic guanidine derivatives led to discontinuation of the Synthalins by the early 1930s (1-31).

CONCLUSION

Metformin, a novel antidiabetic drug of botanical origin has been successfully used as an antidiabetic drug (1922-2022). Metformin was introduced to treat type-2 diabetes in France in 1958 and now used on a daily basis by over 150 million people. Metformin was first synthesized in 1922 and its development was based on knowledge from folk medicine that the active, but toxic, constituent from *Galega officinalis*. Metformin was discovered, forgotten, rediscovered, repurposed, rejected, and rescued. Its botanical history is linked to *Galega officinalis* (also known as goat's rue), a traditional herbal medicine in Europe, found to be rich in guanidine, which, in 1918, was shown to lower blood glucose. Galegine, a guanidine derivative, has been shown to be synthesised in the seedlings, leaves, flowers, and fruits of *Galega officinalis*. Therefore, natural source of galegine, which is a precursor of metformin is widely used as an oral antidiabetic agent. Diabetes is an important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas. Metformin after its introduction in diabetes treatment, has become the most prescribed glucose-lowering medicine worldwide with the potential for further therapeutic applications.

REFERENCES

1. Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. Diabetes Care. 1989; 12: 553–564.
2. Bailey CJ, Day C. Metformin: Its botanical background. Pract Diab Int. 2004; 21 (3): 115-117.
3. Hermann LS. Metformin: A review of history, Pharmacodynamics and therapy. Diabetes Metab Rev. 1979; 5: 233–245.
4. Schafer G. Biguanides: A review of history, pharmacodynamics and therapy. Diabetes Metab Rev. 1983; 9: 148–163.
5. Howlett HCS, Bailey CJ. A risk–benefit assessment of Metformin in type 2 diabetes mellitus. Drug Safety. 1999; 20: 489–503.
6. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreoli F. Cellular and molecular mechanisms of Metformin: An overview. Journal of Clinical Science. 2012; 122(6):253-270.
7. Hariharan M, Rajan SS, Srinivasan, R. Structure of Metformin hydrochloride. Acta Cryst. 1989; 45(6):911-913.
8. Cusi K, Defronzo, RA. Metformin: A review of its metabolic effects. Diabetes Review. 1998; 6:89-131.
9. Rhee CM, Kovesdy CP, Kalantar-Zadeh K. Risks of metformin in type 2 diabetesand chronic kidney disease: Lessons learned from Taiwanese data. Nephron Clinical ractice October 26, 2016.
10. Mori A, Cohen BD, Lowenthal A (eds). Guanidines – Hstorical, biological, biochemical and clinical aspects of the naturally occurring guanidine compounds. London: Plenum Press, 1985.
11. Culpeper N. Culpeper's colour herbal. Potterton D (ed). London: Foulsham & Co Ltd, 1983.
12. Culpeper N. The English Physitian or an astrologo-physical discourse on the vulgar herbs of this nation. London: Peter Cole, 1652.
13. Leclerc H. Le galega. Paris: Presse Med, 22 Dec 1928.
14. Parturier G, Hugnot G. Le galega dans le traitement du diabete. Paris: Masson, 1935.
15. Muller H, Rheinwein H. Pharmacology of galegin. Arch Exp Path Pharmacol. 1927; 125: 212–228.
16. Simonnet H, Tanret G. Sur les propietes hypoglycemiantes du sulfate de galegine. Bull Soc Chim Biol Paris. 1927; 8. 14.
17. Sterne J. Pharmacology and mode of action of the hypoglycaemic guanidine derivatives. In Oral hypoglycaemic agents. Campbell GD (ed). London: Academic Press. 1969; 193–245.
18. Hesse G, Taubmann G. Die Wirkung des Biguanids und seiner Derivate auf den Zuckerstoffwechsel. Naunyn- Schmiedebergs. Arch Exp Path Pharmacol. 1929; 142: 290–308.
19. Slotta KH, Tsesche R. Uber biguanide. II. Die blutzuckersenkende Wirkung der Biguanides. Ber Dtsch Chem Ges. 1929; 62: 1398–1405.
20. Sterne J. Du nouveau dans les antidiabetiques. La NN dimethylamine guanyl guanide (N.N.D.G.). Maroc Med. 1957; 36: 1295–1296.
21. Mehnert H, Seitz W. Weitere Ergebnisse der diabetes behandlung mit blutzuckersenkenden biguaniden. Munch Med Wschr. 1958; 100: 1849–1851.
22. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycaemic drug. Proc Soc Exp Biol Med. 1957; 100: 190–192.
23. English P, Williams G. Hyperglycemic crises and lactic acidosis in diabetes mellitus. Journal of Postgraduate Medicine. 2004; 80:253-261.
24. Hager R, Pitsch J, Kerbl-Knapp J, Neuhauser C, Ollinger, N, Iken M, Ranner J, Mittermeier-Kleßinger V, Dawid C, Lanzerstorfer P, et al. A High-Content screen for the identification of plant extracts with insulin secretion-modulating activity. Pharmaceuticals. 2021; 14: 809. (https:// doi.org/10.3390/ph14080809).
25. Keeler RF, Johnson AE, Stuart LD. Toxicosis from and possible adaptation to Galega officinalis in sheep and the relationship to verbesina encelioides toxicosis. Vet. Hum. Toxicol. 1986; 28, 309–315.
26. Bednarska K, Kus P, Fecka I. Investigation of the Phytochemical Composition, Antioxidant Activity, and Methylglyoxal Trapping Effect of Galega officinalis L. Herb In Vitro. Molecules. 2020; 25: 5810; (doi:10.3390/molecules25245810).
27. Mohammed I, Hollenberg MD, Ding H and Triggle CR. A Critical review of the evidence that Metformin is a putative anti-Aging drug that enhances health span and extends Lifespan. Front. Endocrinol. 2021; 12:718942. (doi: 10.3389/fendo.2021.718942).

28. Bailey CJ. Metformin: Historical overview. Diabetologia. 2017; 60:1566–1576. (DOI 10.1007/s00125-017-4318-z).
29. Perla V, Jayanty SS. Biguanide related compounds in traditional antidiabetic functional foods. Food Chemistry. 2013; 138 : 1574–1580.
30. Reuter G. On guanidine metabolism in Galega officinalis. Phytochemistry. 1962; 1: 63–65.
31. Oldham, Michelle, "Goatsrue (Galega officinalis) Seed Biology, Control, and Toxicity" (2009). All Graduate Theses and Dissertations. UTAH STATE UNIVERSITY Logan, Utah, USA 2009; 235. (https://digitalcommons.usu.edu/etd/235).
32. Malabadi RB, Chalannavar RK, Meti NT, Vijayakumar S, Mulgund GS, Gani RS, Supriya S, Sowmyashree K, Nityasree BR, Chougale A, Divakar MS. Antidiabetic Plant, Gymnema sylvestre R. Br., (Madhunashini): Ethnobotany, Phytochemistry and Pharmacological Updates. International Journal of Current Trends in Pharmacobiology and Medical Sciences. 2016; 1(4):1-17.
33. Malabadi RB, Chalannavar RK, Meti NT, Gani RS, Vijayakumar S, Mulgund GS, Masti S, Chougale RB, Odhav B, Sowmyashree K, Supriya S, Nityasree BR, Divakar MS. Insulin Plant, Costus speciosus: Ethnobotany and Pharmacological Updates. International Journal of Current Research in Biosciences and Plant Biology. 2016; 3(7):151-161.
34. Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TPA. Indian herbs and herbal drugs used for the treatment of Diabetes. J. Clin. Biochem. Nutr. 2007; 40: 163–173.
35. Ramachandran A, Snehalatha C, Viswanathan V. Burden of type 2 diabetes and its complications- the Indian scenario. Curr. Sci. 2002; 83:1471–1476.
36. Acharya M, Divakar MS, Malabadi RB, Chalannavar RK. Ethnobotanical survey of medicinal plants used by the "Nalike" community in the Bantwala taluk of Dakshina Kannada district, Karnataka, India. Plant Science Today (Early Access). https://doi.org/10.14719/ pst.1470.
37. Malabadi RB, Mulgund GS, Nataraja K. Ethanobotanical survey of medicinal plants of Belgaum district, Karnataka, India. Journal of Medicinal and Aromatic Plant Sciences. 2007;29 (2):70-77.
38. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Role of botanical essential oils as a therapy for controlling Coronavirus (SARS-CoV-2) disease (Covid-19). International Journal of Research and Scientific Innovations.2021e; 8(4): 105-118. 87.
39. Malabadi RB, Meti NT, Chalannavar RK. Role of herbal medicine for controlling coronavirus (SARS-CoV-2) disease (COVID-19). International Journal of Research and Scientific Innovations. 2021a; 8(2): 135-165.
40. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Traditional herbal folk medicine used for controlling coronavirus (SARS CoV-2) disease (Covid-19). International Journal of Innovation Scientific Research and Review. 2021b; 3 (7): 1507-1517.
41. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Outbreak of Coronavirus (SARS-CoV-2) Delta variant (B.1.617.2) and Delta Plus (AY.1) with fungal infections, Mucormycosis: Herbal medicine treatment. International Journal of Research and Scientific Innovations. 2021c; 8(6): 59-70.
42. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Vaccine development for coronavirus (SARS-CoV-2) disease (Covid 19): Lipid nanoparticles. International Journal of Research and Scientific Innovations. 2021d; 8(3): 189-195. 86.
43. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Role of plant based hand sanitizers during the recent outbreak of coronavirus (SARS-CoV-2) disease (Covid-19). Significances of Bioengineering & Biosciences. 2021f; 5(1): 458-46.
44. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Camphor tree, Cinnamomum camphora (L.); Ethnobotany, and pharmacological updates. Biomedicine. 2021;41 (2): 181-184.
45. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Triphala: An Indian Ayurvedic herbal formulation for coronavirus (SARS-CoV-2) disease (Covid-19). Int. J. Curr. Res. Biosci. Plant Biol. 2921; 8(8): 18-30. doi: https://doi.org/10.20546/ijcrbp.2021.808.003.
46. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. Melatonin: One molecule one-medicine for many diseases, coronavirus (SARS-CoV-2) disease (Covid-19); Function in plants. International Journal of Research and Scientific Innovations. 2921; 8(3): 155- 181.
47. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. The Iconic Baobab (Adansonia digitata L.): Herbal medicine for controlling Coronavirus (SARS-CoV-2) disease (Covid-19). International Journal of Innovation Scientific Research and Review. 2021; 3(8): 1635-1647.
48. Malabadi RB, Kolkar KP, Meti NT, Chalannavar RK. An Age old Botanical weapon for Herbal therapy: Camphor tree, Cinnamomum camphora. International Journal of Innovation Scientific Research and Review. 2021; 3(7): 1518-1523.

****