Chapter 2: Review of Literature

2.1. Diabetes

Diabetes is the most severe and prevalent chronic disorder, causing shortened life expectancy and potentially fatal complications and affecting individuals of nearly all age groups (Abdullah et al., 2021; Heald et al., 2020). It arises from the body's inability to properly process and regulate blood glucose levels, either due to insufficient insulin production by the pancreas or the inability of insulin to regulate blood sugar effectively. Insulin is a polypeptide hormone that is produced and secreted by the beta-cells of the islets of Langerhans situated in the pancreas; it plays a critical role in maintaining blood glucose levels by facilitating the assimilation and utilization of glucose by the body's cells. In individuals with diabetes, a condition known as "insulin resistance" often occurs (Campbell and Newgard, 2021; Dimitriadis et al., 2021). When body's cells inefficiently respond to insulin by lesser sensitivity, the situation is termed as insulin resistant, ultimately leading to a diminished effect of the hormone on glucose metabolism (Saltiel and Kahn, 2001). This decrease in sensitivity to insulin's biochemical actions, including insulin-mediated glucose disposal, results in a buildup of glucose in the bloodstream, which can eventually lead to type 2 diabetes (Ross et al., 2004).

According to estimates, diabetes has reached a pandemic, and there are 536.6 million diabetic people worldwide in 2021, which is anticipated to climb to 783.2 million by 2045 (Sun et al., 2022). International Diabetes Federation 2021 (10th edition) reported that India would have 74.2 million people with diabetes by 2021, which would rise to 124.9 million by 2045 (diabetesatlas.org) (Parikh et al., 2024). Diabetes is a significant global health issue, with current estimates indicating that over half a billion people live with the condition, accounting for more than 10.5% of the global adult population. Diabetes can result from various factors, and its management depends on the specific type of diabetes

(Saeedi et al., 2019). While there are several forms of diabetes, the three main types are Type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus, as represented in Figure 2.1 (Xiang et al., 2018).

2.1.1 Types of Diabetes:

2.1.1.1 Type 1 Diabetes (T1DM)

The hallmark of T1DM is inadequate insulin synthesis, which leads to hyperglycemia, which arises from the autoimmune destruction of pancreatic beta cells, leading to a complete lack of insulin (Li et al., 2014; Thomas and Philipson, 2015).

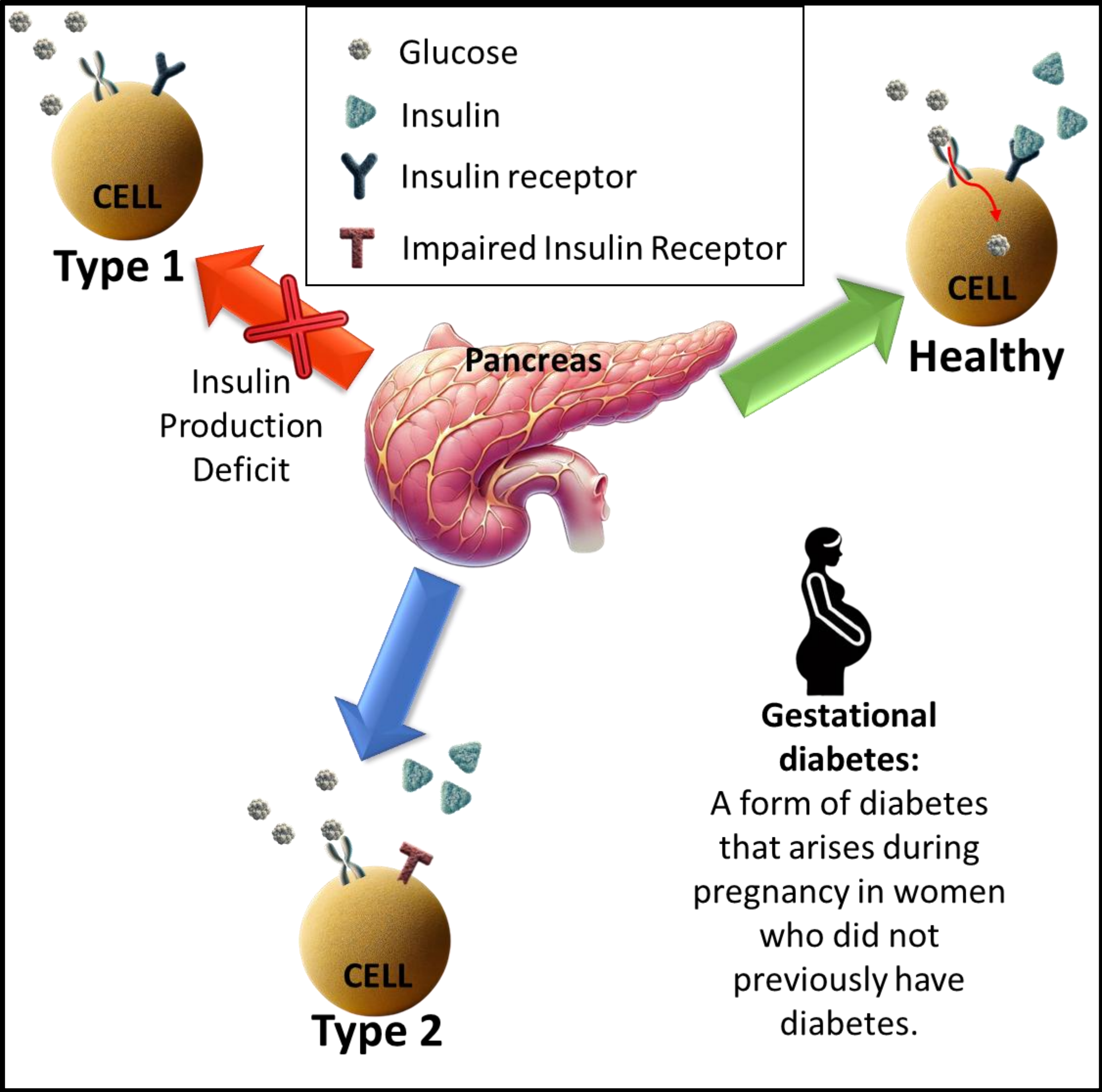

Figure 2.1: Classification of Diabetes Mellitus

T1DM requires careful management to avoid major complications, such as cardiovascular and kidney diseases, vision loss, and stroke (Akil et al., 2021) The primary treatment for T1DM is insulin therapy, known as “exogenous insulin replacement therapy.” However, many individuals find it challenging to achieve optimal blood glucose control with this approach alone (Katsarou et al., 2017).

2.1.1.2 Type 2 Diabetes (T2DM)

T2DM is a widespread type of diabetes caused by two primary factors: the body's tissues' incapacity to respond to insulin and the pancreatic β-cells' insufficient release of insulin (Muoio and Newgard, 2008). Risk factors for T2DM include elevated blood glucose levels, obesity, high triglycerides, poor dietary habits, lack of physical activity, aging, genetic predisposition, stress, anxiety, and depression. Treatment and management typically involve a combination of insulin therapy, metformin, and other glucose-lowering medications (Bi et al., 2012; Mosenzon et al., 2021).

2.1.1.3 Gestational Diabetes (Pregnancy-Induced Diabetes)

Hyperglycemia during pregnancy is a hallmark of gestational diabetes mellitus (GDM). It can affect both the mother and the baby and is typically diagnosed in women with no prior history of diabetes (McIntyre et al., 2019). Factors that contribute to the development of GDM include obesity, a family history of diabetes, and advanced maternal age. This condition is related to an increased risk of T2DM and ischemic heart disease. It is the most common pregnancy complication and usually emerges in the second or third trimester. Management strategies include insulin therapy and lifestyle modifications, such as nutritional therapy (Li et al., 2020).

The most important characteristics of all kinds of diabetes are hyperglycemia and hyperlipidemia, and their persistence causes several consequences, including

atherosclerosis, cardiovascular diseases, diabetic nephropathy, neuropathy, and kidney failure (Agrawal et al., 2022; Ashraf et al., 2022). Deficiency in insulin secretion or ineffective insulin action can cause chronic hyperglycemia with abnormal protein, lipid, and carbohydrate metabolism (Alam et al., 2019; Shahwan et al., 2022).

2.1.2 Physiopathology of Diabetes:

The main characteristic of diabetes is insulin resistance, but T2DM can also be brought on by hereditary and environmental factors. The pathophysiology of diabetes is represented in Figure 2.2, which is closely linked to the body's insulin levels and their effective utilization (Kadayifci et al., 2019). In T1DM, insulin is absent due to autoimmune destruction of pancreatic beta cells (Morran et al., 2015). In contrast, T2DM involves resistance to insulin's effects by peripheral tissues (Fève and Bastard, 2009). The brain, which relies heavily on blood glucose for proper functioning, is regulated by insulin release from pancreatic beta cells in response to elevated blood glucose levels.

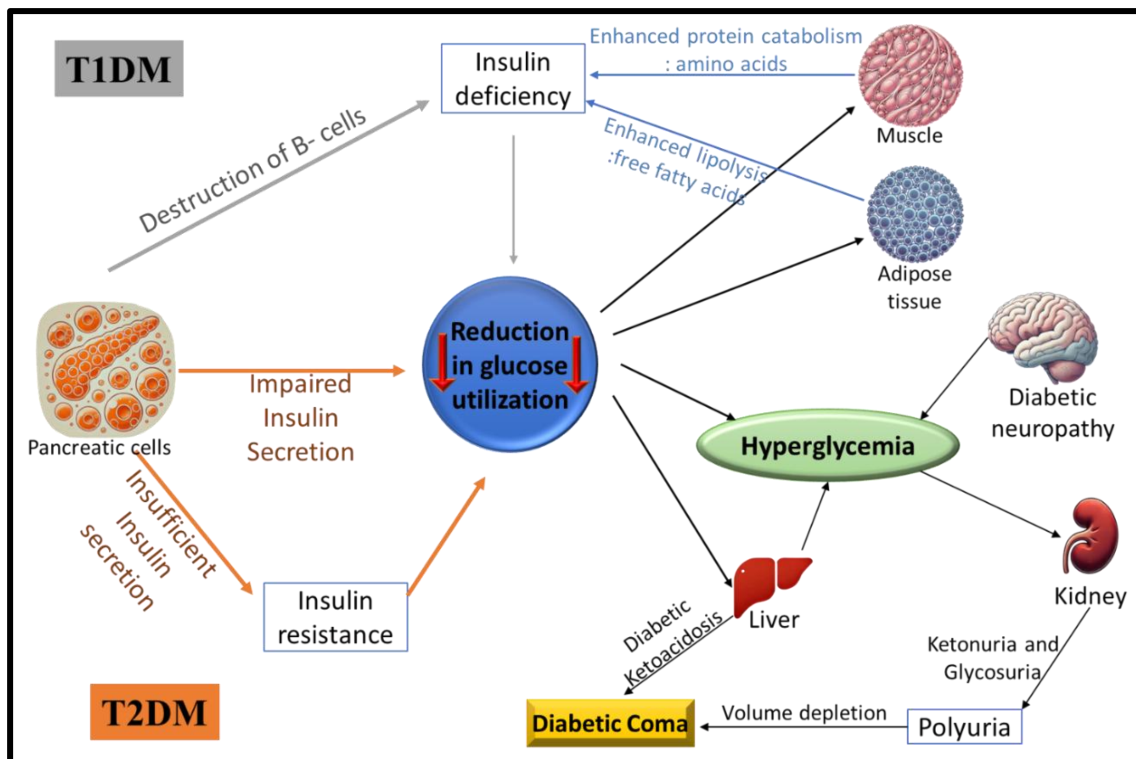

Figure 2.2: Pathophysiology of Diabetes

Hyperglycemia is managed with oral antihyperglycemic agents and insulin therapy (Banks et al., 2012). Glucose levels in the plasma also signal the central nervous system to release energy stores (Cota et al., 2007). Low blood glucose levels trigger an increase in autonomic activity, leading to hypoglycemia, a condition indicative of diabetes. The body's response to hypoglycemia includes reduced insulin secretion, increased release of glucagon and epinephrine (counter-regulatory hormones), heightened sympathoadrenal activity, and in severe cases, cognitive impairment, seizures, stroke, syncope, or coma. Rapid administration of glucose intravenously or orally is an effective treatment to restore normal blood glucose levels (Cryer et al., 2003). In T1DM, the progression of the disease depends on the rate of autoimmune destruction of pancreatic beta cells. Diabetic ketoacidosis (DKA) is a serious complication of diabetes, characterized by the rapid breakdown of fat, leading to ketone production by the liver and resulting in blood acidosis. DKA commonly occurs in children and young adults due to beta cell destruction and is often the first manifestation of T1DM (Balaji et al., 2019). The disease progresses slowly, with a gradual increase in fasting plasma glucose levels. As insulin deficiency worsens, patients become dependent on insulin to manage severe hyperglycemia and ketoacidosis, ultimately requiring lifelong insulin therapy for survival (Davies et al., 2018).

T2DM is characterized by both insulin resistance and insulin deficiency. These factors are associated with elevated inflammatory cytokines and high levels of fatty acids, which impair glucose transport into cells, increase fat breakdown, and elevate hepatic glucose production (Muoio and Newgard, 2008). Hyperglycemia results from excessive glucagon secretion by alpha cells and insufficient insulin production by beta cells. T2DM is diagnosed when patients are unable to increase insulin secretion to compensate for insulin resistance, leading to elevated blood glucose levels (Lund et al., 2014).

T2DM may remain undiagnosed in its early stages because it progresses slowly and is initially asymptomatic, with only mild hyperglycemia. Symptoms such as excessive thirst (polydipsia), weight loss, blurred vision, and growth impairment often appear in the later stages (Balaji et al., 2019). The development of T2DM involves a combination of genetic predisposition and environmental influences, including poor diet, aging, sedentary lifestyle, family history of diabetes, obesity, previous gestational diabetes in women, and associated conditions like atherosclerosis, dyslipidemia, and hypertension (Halpern et al., 2010).

GDM is diagnosed when glucose intolerance is first identified during the second or third trimester of pregnancy. Early in pregnancy, fasting and random blood glucose levels are typically lower than normal. However, a significant increase in blood glucose during the third trimester confirms the presence of gestational diabetes mellitus (Seshiah et al., 2007).

2.1.3 Management of Diabetes

The main goals of diabetes medications are blood glucose regulation and the avoidance of hyperglycemia-related complications. Treatment approaches differ between T1DM and T2DM but share common goals of maintaining blood glucose within a normal range. An overview of therapeutic approaches for managing Diabetes Mellitus is represented in Figure 2.3. Below is a summary of the key drugs used to treat diabetes:

2.1.3.1 Insulin Therapy

Insulin therapy is essential for individuals with T1DM and is also used in some cases of T2DM when other medications are insufficient to control blood glucose levels. Insulin is a hormone necessary for glucose uptake by cells, and in people with T1DM, the body does not produce insulin due to the autoimmune destruction of pancreatic beta cells (Salsali and Nathan, 2006). Various forms of insulin are used, each differing in onset and

duration of action. Rapid-acting insulins like insulin lispro, short-acting insulins such as regular insulin, intermediate-acting insulins like NPH, and long-acting insulins such as insulin glargine provide different levels of glucose control throughout the day. The goal of insulin therapy is to mimic natural insulin secretion, maintaining blood glucose levels within a normal range to prevent hyperglycemia and associated complications (Lepore et al., 2000).

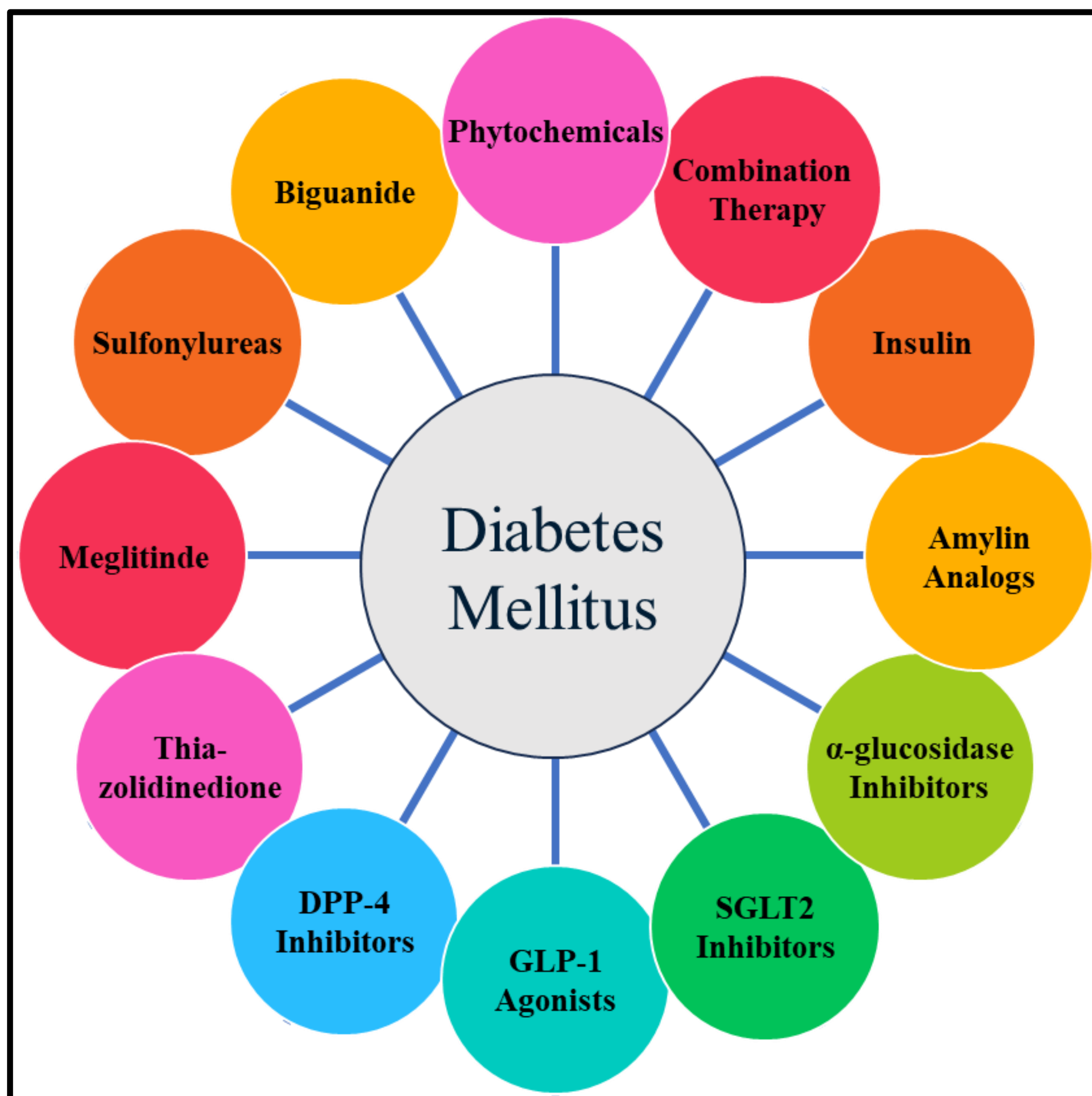

Figure 2.3: Overview of therapeutic approaches for managing Diabetes Mellitus.

2.1.3.2 Oral Medications

Oral medications are commonly used in managing T2DM, where insulin resistance and relative insulin deficiency are prevalent. Biguanides, with metformin being the most

widely used, work by reducing hepatic glucose production and improving insulin sensitivity. Sulfonylureas, like glimepiride, stimulate the pancreas to release more insulin, whereas meglitinides, such as repaglinide, also promote insulin secretion but have a shorter duration of action. Thiazolidinediones, like pioglitazone, improve insulin sensitivity in fat and muscle tissues. DPP-4 inhibitors, such as sitagliptin, and SGLT2 inhibitors, like empagliflozin, target different mechanisms to enhance insulin secretion and reduce glucose reabsorption, respectively. These medications are often used in combination to achieve better glycemic control and address multiple pathways of glucose regulation (Alhadramy, 2016; He et al., 2015; Padhi et al., 2020).

2.1.3.3 Non-Insulin Injectable Medications

In addition to insulin, non-insulin injectable medications are also crucial in diabetes management, especially for T2DM. GLP-1 receptor agonists mimic the incretin hormone GLP-1, which ultimately helps in enhancing insulin secretion, suppressing glucagon secretion, gastroparesis, and promoting satiety. These actions aid in weight loss in addition to lowering blood glucose levels, making them particularly beneficial for overweight individuals with T2DM. Another injectable option is pramlintide, an amylin analogue, which works alongside insulin to regulate postprandial blood glucose by gastroparesis and reducing glucagon release (Nauck et al., 2021; Sharma et al., 2018).

2.1.3.4 Combination Therapies

Combination therapies are often necessary for individuals with T2DM to achieve optimal blood glucose control. These therapies involve using two or more medications that work through different mechanisms, providing a synergistic effect. For example, combining metformin with a sulfonylurea or a DPP-4 inhibitor can enhance glucose-lowering effects by both reducing hepatic glucose production and increasing insulin secretion (Ahren, 2008; Kuritzky and Samraj, 2011). Insulin can also be combined with oral medications

or non-insulin injectables to target different aspects of glucose metabolism and insulin resistance (Scheen et al., 1993). Combination treatments can enhance overall diabetes care and lower the chance of complications (Evert et al., 2014).

2.1.3.5 Emerging Therapies

Emerging therapies for diabetes management offer additional options for individuals who may not respond well to traditional treatments. Bile acid sequestrants, like colesevelam, primarily used to lower cholesterol, have shown modest glucose-lowering effects and can be used in conjunction with other diabetes medications (Staels and Kuipers, 2007). Dopamine agonists, such as bromocriptine, work by modulating the hypothalamic regulation of metabolism, improving insulin sensitivity. These emerging therapies provide alternative mechanisms for managing blood glucose levels, offering hope for better control and quality of life for people with diabetes. As research continues, new drugs and treatment approaches will likely become available, further enhancing diabetes care (Tavares et al., 2021).

2.1.4 Medicinal plants in the management of diabetes

Medicinal plants play a significant role in managing diabetes by offering natural alternatives or complementary therapies to conventional treatments. They regulate blood glucose levels, enhance insulin sensitivity, and protect against diabetes-related complications (Unuofin and Lebelo, 2020). A list of medicinal plants with therapeutic roles in diabetes management is represented in Table 2.1. Plants like *Gymnema sylvestre* and *Momordica charantia* can lower blood sugar by reducing sugar absorption and stimulating insulin secretion (Yadav et al., 2010). *Cinnamomum cassia* (cinnamon) and *Pterocarpus marsupium* have been shown to enhance insulin receptor function and sensitivity, aiding glucose uptake by cells. They also inhibit carbohydrate-digesting enzymes, slowing glucose absorption and preventing post-meal blood sugar spikes

(Choudhury et al., 2018). *Salacia reticulata* and *Phyllanthus amarus* inhibit α-A and α-G (Bhatia et al., 2022). Moreover, plants like *Trigonella foenum-graecum* (fenugreek) and *Allium sativum* (garlic) promote insulin secretion, enhancing blood glucose regulation (Pradeep and Srinivasan, 2017). Furthermore, plants such as *Vaccinium myrtillus* (bilberry) and Ginkgo biloba offer protection against diabetic complications like retinopathy and neuropathy, ensuring comprehensive diabetes management (Saxena et al., 2022).

Table 2.1: List of Medicinal plants with antidiabetic activity

Plant Name	Family	Plant Part Used	Reference
Gymnema sylvestre	Apocynaceae	Leaves	(Rahman and Husen, 2023)
Momordica charantia	Cucurbitaceae	Fruit, Leaves	(Banerjee et al., 2019)
Curcuma longa	Zingiberaceae	Rhizome	(Mohammed et al., 2017)
Salacia reticulata	Celastraceae	Root, Stem	(Peiris et al., 2023)
Camellia sinensis	Theaceae	Leaves	(Ardiana et al., 2018)
Zingiber officinale	Zingiberaceae	Rhizome	(G. Kumar et al., 2011)
Cinnamomum cassia	Lauraceae	Bark	(Vijayakumar et al., 2023)
Syzygium cumini	Myrtaceae	Seeds, Leaves	(Schoenfelder et al., 2010)
Pterocarpus marsupium	Fabaceae	Bark	(Maruthupandian and Mohan, 2011)
Berberis vulgaris	Berberidaceae	Root, Bark	(Dulić et al., 2019)
Azadirachta indica	Meliaceae	Leaves, Bark	(Arika et al., 2016)
Coccinia grandis	Cucurbitaceae	Leaves, Fruits	(Putra et al., 2021)
Mangifera indica	Anacardiaceae	Leaves, Bark	(Samanta et al., 2019)
Phyllanthus emblica	Phyllanthaceae	Fruit	(Pathak et al., 2016)
Morus alba	Moraceae	Leaves, Bark	(Zhou et al., 2022)
Psidium guajava	Myrtaceae	Leaves	(Oh et al., 2005)
Ficus religiosa	Moraceae	Leaves, Bark	(Choudhary et al., 2011)
Tinospora cordifolia	Menispermaceae	Stem	(Rajalakshmi et al., 2009)
Moringa oleifera	Moringaceae	Leaves	(Chen et al., 2020)
Nigella sativa	Ranunculaceae	Seeds	(Mofio et al., 2020)
Ocimum basilicum	Lamiaceae	Leaves	(Kadan et al., 2016)
Phaseolus vulgaris	Fabaceae	Seeds	(Ezzat et al., 2022)
Terminalia arjuna	Combretaceae	Bark	(Shengule et al., 2018)
Helianthus annuus	Asteraceae	Seeds	(Onoja and Anaga, 2014)
Rauvolfia serpentina	Apocynaceae	Root	(Surendran et al., 2021)

Annona squamosa	Annonaceae	Leaves, Seeds	(Gupta et al., 2005)
Allium cepa	Amaryllidaceae	Bulbs	(Sabiu et al., 2019)
Curcuma amada	Zingiberaceae	Rhizome	(Mitra et al., 2019)
Emblica officinalis	Phyllanthaceae	Fruit	(Saini et al., 2022)
Salvia officinalis	Lamiaceae	Leaves	(Eidi and Eidi, 2009)
Tamarindus indica	Fabaceae	Fruit	(Roy et al., 2010)
Vernonia amygdalina	Asteraceae	Leaves	(Ajayi et al., 2021)
Zea mays	Poaceae	Seeds, Silk	(Sabiu et al., 2016)
Achyranthes aspera	Amaranthaceae	Root, Leaves	Chandra et al., 2007
Ajuga bracteosa	Lamiaceae	Whole plant	(Hafeez et al., 2017)
Alangium salvifolium	Alangiaceae	Leaves, Bark	(Ratra and Gupta, 2015)
Bixa orellana	Bixaceae	Seeds	(Tonny et al., 2024)
Buchanania lanzan	Anacardiaceae	Leaves	(Sushma et al., 2013)
Calotropis procera	Apocynaceae	Leaves	(Neto et al., 2013)
Coleus forskohlii	Lamiaceae	Root	(Venkatachalapathi et al., 2019)
Costus igneus	Costaceae	Leaves	(Aruna et al., 2014)
Dalbergia sissoo	Fabaceae	Leaves, Bark	(Panda et al., 2016)
Eleusine indica	Poaceae	Leaves	(Adoho et al., 2021)
Erythrina variegata	Fabaceae	Leaves	(A. Kumar et al., 2011)
Hibiscus sabdariffa	Malvaceae	Calyx	(Bule et al., 2020)

2.1.5 Phytoconstituents in the Management of Diabetes

Phytoconstituents, which are bioactive compounds found in plants, play a significant role in the management of diabetes through various mechanisms. Flavonoids, alkaloids, phenolic compounds, glycosides, tannins, saponins, steroids, and terpenoids are various classes of phytoconstituents that exhibit antidiabetic activity and have been listed in **Table 2.2.**

Table 2.2: Phytoconstituents in the Management of Diabetes.

Phytoconstituent	Class of Phytoconsti-tuent	Effects in Diabetes Management	References
Quercetin	Flavonoid	Enhances insulin secretion and sensitivity	(Abdou et al., 2022)
Resveratrol	Polyphenol	Enhances insulin sensitivity via AMPK activation	(Vlavcheski et al., 2020)
Berberine	Alkaloid	Inhibits α-A and α-G, reduces glucose	(Das et al., 2023)
Epigallocatechin gallate (EGCG)	Polyphenol	Inhibits carbohydrate-digesting enzymes, reduces glucose spikes	(Shahidi and Danielski, 2024)

Curcumin	Polyphenol	Reduces oxidative stress and inflammation, inhibits NF-κB	(Zamanian et al., 2024)
Lycopene	Carotenoid	Antioxidant, reduces oxidative stress associated with diabetes	(Eze et al., 2018)
Anthocyanins	Flavonoid	Antioxidant, reduces oxidative stress, improves glucose uptake	(Sancho and Pastore, 2012)
Naringenin	Flavonoid	Improves lipid profile, reduces triglycerides and LDL levels	(Den Hartogh and Tsiani, 2019)
Hesperidin	Flavonoid	Reduces blood glucose and improves lipid metabolism	(Sundaram et al., 2019)
Rutin	Flavonoid	Antioxidant, improves glucose tolerance	(Ghorbani, 2017)
Apigenin	Flavonoid	Reduces oxidative stress, improves glucose metabolism	(Ren et al., 2016)
Luteolin	Flavonoid	Inhibits inflammation, enhances insulin sensitivity	(Ding et al., 2010)
Fisetin	Flavonoid	Improves glucose metabolism, reduces inflammation	(Prasath et al., 2014)
Scutellarin	Flavonoid	Antioxidant, improves insulin resistance	(Huo et al., 2021)
Silymarin	Flavonoid	Antioxidant, improves liver function, reduces blood glucose	(Elgarf et al., 2015)
Isorhamnetin	Flavonoid	Antioxidant, improves glucose uptake	(Alqudah et al., 2023)
Morin	Flavonoid	Enhances glucose uptake, antioxidant	(Ola et al., 2014)
Diosmin	Flavonoid	Reduces blood glucose, antioxidant	(Srinivasan and Pari, 2012)
Limonene	Terpenoid	Reduces blood glucose levels, improves lipid profile	(Murali and Saravanan, 2012)
Linalool	Terpenoid	Reduces blood glucose levels, antioxidant	(Bar and Kara, 2024)
Pinene	Terpenoid	Antioxidant, improves glucose uptake	(Santos et al., 2023)
Rosmarinic Acid	Polyphenol	Antioxidant, reduces oxidative stress	(Topal and Gulcin, 2022)
Caffeic Acid	Polyphenol	Antioxidant, improves glucose metabolism	(Xu et al., 2020)
Gallic Acid	Polyphenol	Reduces blood glucose, improves lipid profile	(Xu et al., 2021)
Ellagic Acid	Polyphenol	Reduces blood glucose levels, antioxidant	(Fatima et al., 2017)
Vanillic Acid	Polyphenol	Antioxidant, improves glucose uptake	(Chang et al., 2015)
Pterostilbene	Polyphenol	Antioxidant, improves lipid profile	(Kosuru and Singh, 2017)
Oleanolic Acid	Triterpenoid	Reduces blood glucose, improves insulin sensitivity	(Wang et al., 2011)
Ursolic Acid	Triterpenoid	Antioxidant, reduces blood glucose levels	(Castellano et al., 2013)
Asiatic Acid	Triterpenoid	Antioxidant, reduces blood glucose levels	(Ramachandran and Saravanan, 2013)
Maslinic Acid	Triterpenoid	Reduces blood glucose, improves	(Liu et al., 2007)

		insulin sensitivity	
Piperine	Alkaloid	Enhances glucose uptake, reduces insulin resistance	(Prasad et al., 2023)
Capsaicin	Alkaloid	Reduces blood glucose levels, improves lipid profile	(S. Zhang et al., 2017)

2.2 Cancer

Globally, cancer is known as one of the most prevalent causes of morbidity and death. As per the Globocan 2020 study, a death toll of 10 million by cancer and 19.3 million new cancer cases were reported worldwide (Sung et al., 2021). This data is later proceeded by the International Agency for Research on Cancer (IARC) stating this figures would increase to 13.2 million yearly fatalities and 22.2 million new cases by 2030 (Shimbre et al., 2019). These alarming statistics underscore the urgent need for novel therapeutic targets, more effective diagnostic biomarkers, and improved treatment strategies. Recent advances in cancer research have highlighted key oncogenic pathways, including those involving cell signaling, apoptosis, cell cycle checkpoints, and histone modifications. Understanding these pathways is crucial for elucidating cancer development (Lapenna and Giordano, 2009). However, many of these pathway components are intracellular, presenting challenges for therapeutic targeting and making them less suitable as diagnostic biomarkers. There is a pressing need to identify novel, more accessible targets that can serve as reliable clinical biomarkers and be utilized in targeted drug delivery systems. Additionally, efforts to reduce the dosages of current cancer treatments are vital to minimize severe side effects, thereby improving patient outcomes and quality of life.

Breast cancer is more prevalent in women, while prostate cancer is more frequent in men (Gucalp et al., 2019). The most widespread cancers in children are blood cancers, brain tumors, and lymph node tumors (Seth and Singh, 2015). Sarcomas, myeloma, lymphoma, leukemia, carcinomas, and malignancies of the brain and spinal cord are among the several forms of cancer. Adenocarcinoma, squamous cell carcinoma, basal cell

carcinoma, and transitional cell carcinoma are other classifications for cancers (Koul and Koul, 2019; Luebbers, 2019; Zieren et al., 2019).

Acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) are all known as types of leukemia. An uncontrolled rise in white blood cells (WBC) in the bone marrow is a hallmark of acute leukemia. (Levine et al., 2005; Redaelli et al., 2003). Changes in DNA sequences, abnormalities in gene expression, and chromosomal translocations are the main causes of leukemia. Common symptoms of cancer include unexplained weight loss, recurrent infections, persistent fatigue, breathlessness, bone and joint pain, swollen lymph nodes, and night sweats (Emery et al., 2022; Zhang and Rowley, 2006).

Cancer treatment options vary and include chemotherapy and radiation therapy. Chemotherapy targets the activity of oncogenes, such as the BCR-ABL fusion gene, to reduce the proliferation of malignant cells. Radiation therapy destroys cancer-affected cells by damaging their DNA, thereby preventing their growth and division (Yang and Fu, 2015). Addressing the global cancer burden requires continued research into identifying new biomarkers and therapeutic targets, enhancing early detection methods, and developing more effective and less toxic treatment modalities.

2.2.1 Pathophysiology of Cancer

In Today’s era, cancer has become an intimidating disease to treat and is a leading cause of death worldwide. Unregulated cell proliferation is the primary reason for cancer, resulting in tumor growth in a number of organs. The physiopathology of cancer is represented in Figure 2.4. The majority of cancers originate by genetic modifications, such as gene mutations or DNA damage, brought on by exposure to carcinogens (Basu, 2018; Sadikovic et al., 2008).

The PI3K/mTOR/AKT pathway is a key mechanism implicated in the genetic modification of DNA sequences in cancer (Sharma et al., 2023a). This pathway is significant in many cancers and includes various genetic alterations: 6% PIK3CA amplification, 7% PTEN deletion, 9% PTEN mutation, 4% PIK3R1 mutation, 2% PPP2R1A and TSC1 mutations, 1% STK11 deletion, 3% RICTOR amplification, and 4% MTOR amplification. These mechanisms lead to mutations in DNA and RNA as well as the duplication or deletion of DNA sequences (Y. Zhang et al., 2017).

The PI3K/mTOR/AKT pathway is catalyzed by the interaction of class IA PI3K heterodimers. PI3K is activated by receptor tyrosine kinases (RTKs) through adaptor proteins like IRS1 and IRS2 when it is phosphorylated. The p110 catalytic subunits' activity is modulated by the inhibition of the p85 and p110 subunits caused by the interaction with adaptor proteins in the amino-terminal domain of PI3K. The phosphatidylinositol-4,5-biphosphate (PIP2) is then changed into PIP3 by the p110 heterodimer. Following dephosphorylation, the AKT signaling pathway is triggered, resulting in the encoding of p85 genes, mutations, and the activation of PIK3CA oncogenes (Paplomata and O'Regan, 2014; Zhong et al., 2023).

Following the activation of oncogenes, molecules, including platelet-derived growth factor receptor (PDGFR) and telomerase reverse transcriptase (TERT), are active. The levels of PDGF (platelet-derived growth factor) and MAPK1 (mitogen-activated protein kinase 1) are reduced by this reverse transcription process, which is critical for controlling cell growth. The result is rapid cell proliferation and DNA mutations, including inactivation of the tumor suppressor gene p53, further enhancing cell division and cancer progression (Marei et al., 2021; Pullamsetti et al., 2017). Chromosomal abnormalities associated with these pathways lead to changes in RNA synthesis and ribosomal processing, affecting the cell cycle (Chen et al., 2021; Li et al., 2016).

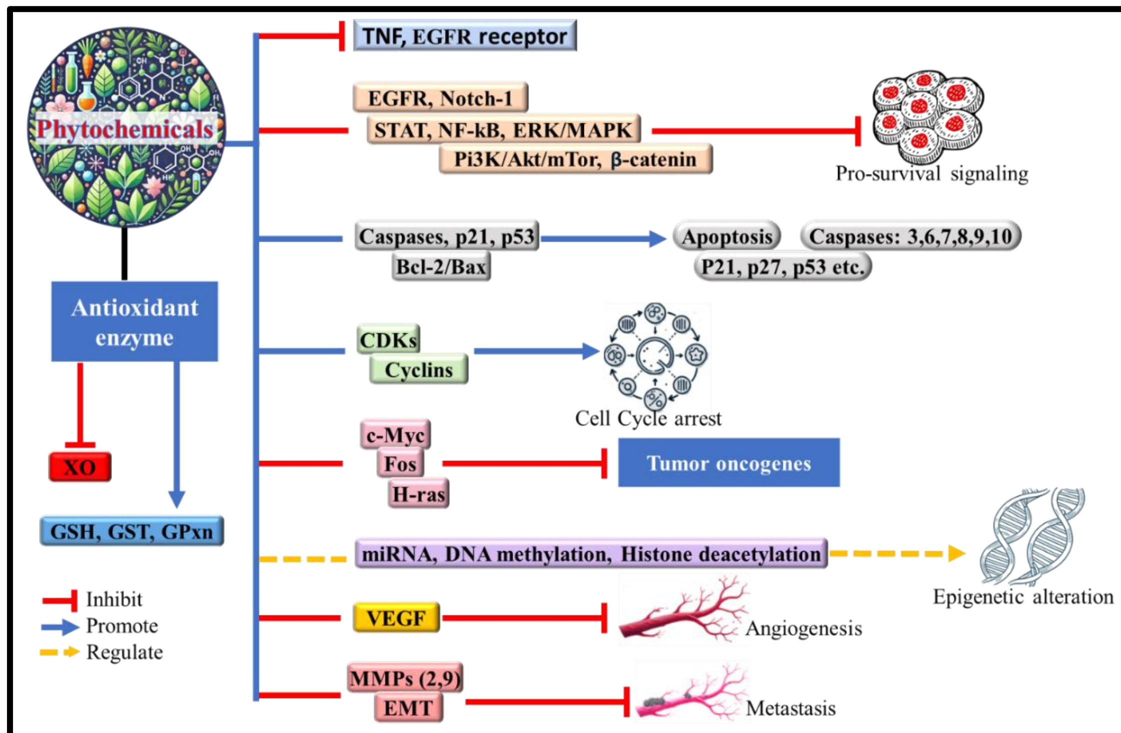

Figure 2.4: Phytochemicals target multiple molecular mechanisms to regulate cancer development and progression.

The activation of the ERK-MAPK and AKT signaling pathways also influences the immune system by boosting CD4+ T cells, natural killer (NK) cells, neutrophils, and G1+ myeloid-derived suppressor cells (MDSCs), as well as encouraging the proliferation of CD8+ T cells. This immune system impairment contributes to the progression of carcinoma (Li et al., 2019; Shen et al., 2019). Gene mutations increase vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6), which also stimulate angiogenesis and tumor growth. (Fiori et al., 2019; Sahai et al., 2020).

The membrane glycoprotein CD36, which is involved in the transfer of fatty acids, has become elevated in gastric cancer, breast cancer, colon cancer, and acute myeloid leukemia. Changes in CD36 protein levels trigger signaling pathways that cause tumor formation, including TGF and hypoxia-induced factor-1 (Sharma et al., 2023b). These tumors spread through the blood and lymphatic systems, contributing to cancer metastasis (Belisario et al., 2020; Zou et al., 2020).

2.2.2 Natural Compounds with Anti-Cancer Properties

Cancer treatment can involve the use of synthetic medications in addition to surgical interventions. Some of the commonly used medications for cancer include abemaciclib, palbociclib, imatinib, and ribociclib. While these synthetic drugs can be effective, they are often expensive and can have significant side effects. These adverse effects may include Myelosuppression, thrombocytopenia, leukopenia, neutropenia, nephrotoxicity, irritation of the mucosal membrane of the mouth, hemoglobin deficiency, significant weight loss (inanition), and general illness with emaciation, diarrhea, and nausea (Cavalu et al., 2024; Pavlovic et al., 2023).

Owing to these limitations, researchers have started looking at natural products that can target particular pathways and interact with different proteins to stop the spread of cancer. Compared to synthetic pharmaceuticals, these natural substances typically have fewer adverse effects, and it's usually easier to isolate chemical compounds from plants than it is to synthesize drugs in a lab. Phytochemicals that regulate cancer processes by inducing apoptosis, inhibiting invasion/metastasis, promoting autophagy, and controlling the cell cycle have been represented in Figure 2.5. Some notable natural compounds with anticancer properties include Quercetin, curcumin, vinblastine, andrographolide, 14-deoxyandrographolide, β-elemene, and baicalein (Nandy and Thakur, 2023).

It has been demonstrated that curcumin, a phytoconstituents isolated from the rhizome of the *Curcuma longa L.* plant, inhibits the transcription factor NF-κB, which triggers apoptosis. (Liczbiński et al., 2020). Another well-known natural compound with anticancer properties is berberine, which is derived from various plant species, including *Berberis aristata, Coptis chinensis*, and *Coptis japonica* (Lamichhane et al., 2014). Berberine affects NF-κB, MMP-2, and MMP-9 and targets important signaling pathways,

including AMPK (adenosine monophosphate-activated protein kinase) and mTOR (mechanistic target of rapamycin).

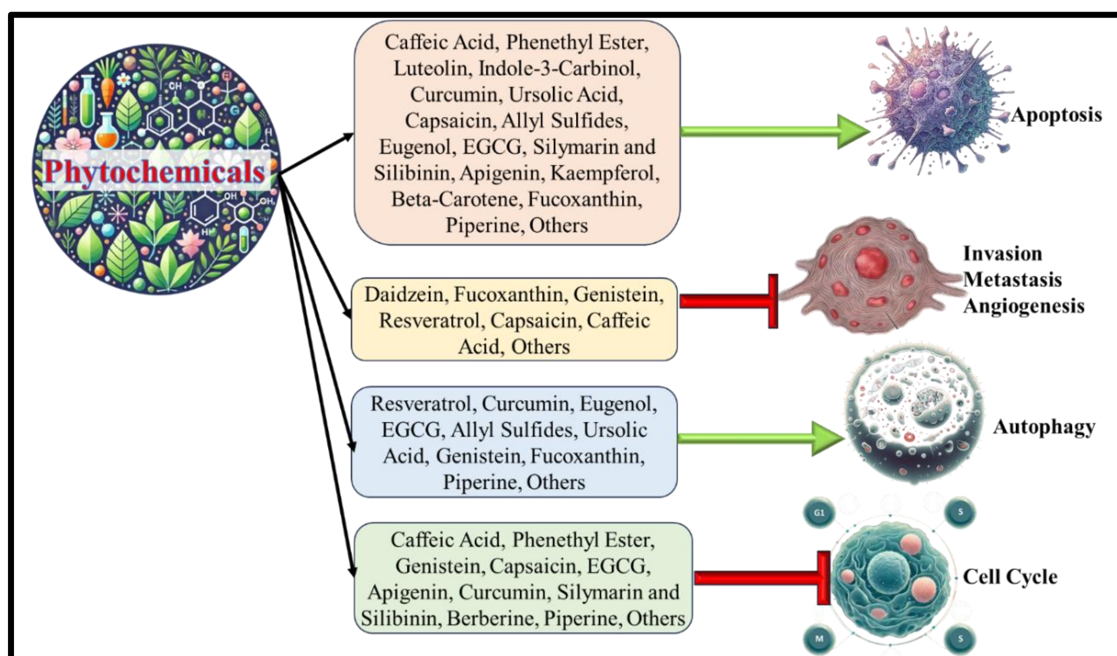

Figure 2.5: Anticancer effects of natural phytochemicals through apoptosis induction, metastasis inhibition, autophagy promotion, and cell cycle control.

By these means, berberine aids in controlling the development of tumors and the proliferation of cells during unregulated cell proliferation (McCubrey et al., 2017). The list of phytochemicals and their targets in cancer therapy has been provided in Table 2.3. These natural compounds offer promising avenues for cancer treatment by directly targeting the mechanisms of tumor formation and cell proliferation, potentially providing safer and more cost-effective alternatives to conventional synthetic drugs.

Table 2.3: Phytochemicals and Their Role in Cancer Therapy: Targets, Mechanisms of Action, and Cancer Types

S.No	Phyto-chemicals	Drug Targets	Treatment for Various Cancer Types	Process of Intervention	References
1	Curcumin	NF-κB, COX-2, STAT3, p53	Breast, Colon, Prostate, Pancreatic	Inhibits inflammation and induces apoptosis by downregulating NF-κB and COX-2, and activating p53	(Wang et al., 2021)

2	Resveratrol	SIRT1, p53, NF-κB, AKT	Breast, Colon, Lung, Prostate	Modulates cell cycle, apoptosis, and inhibits angiogenesis by targeting p53, NF-κB, and SIRT1	(Yang et al., 2022)
3	Epigallocatechin-3-gallate (EGCG)	EGFR, HER2, COX-2, NF-κB	Breast, Lung, Prostate, Skin	Blocks growth signals and induces apoptosis by targeting EGFR, HER2, and NF-κB	(Shimizu et al., 2008)
6	Apigenin	p53, STAT3, PI3K/AKT	Breast, Colon, Skin, Prostate	Induces cell cycle arrest and apoptosis by activating p53 and inhibiting STAT3 and PI3K/AKT signaling	(Abid et al., 2022)
7	Lycopene	IGF-1, RAR-β, NF-κB	Prostate, Lung, Stomach	Inhibits cancer progression by downregulating IGF-1 and NF-κB and modulating retinoid pathways	(Palozza et al., 2011)
8	Berberine	AMPK, p53, mTOR	Breast, Colon, Prostate, Liver	Activates AMPK and p53 pathways to inhibit mTOR signaling, leading to reduced cell proliferation and survival	(Huang et al., 2021)
9	Sulforaphane	Nrf2, HDAC, HSP90	Breast, Prostate, Lung, Colon	Enhances antioxidant response, inhibits histone deacetylases, and induces heat shock proteins	(Tortorella et al., 2015)
10	Indole-3-carbinol	ER, AR, CYP1A1	Breast, Prostate, Cervical, Ovarian	Modulates estrogen and androgen receptors, induces detoxifying enzymes	(Reyes-Hernández et al., 2023)
11	Thymoquinone	NF-κB, STAT3, p53, Bcl-2	Breast, Colon, Prostate, Pancreatic	Inhibits inflammation and tumor growth by modulating NF-κB, STAT3, and apoptosis pathways	(Junaid et al., 2021)
12	Kaempferol	HER2, VEGF, Bcl-2	Breast, Ovarian, Lung, Bladder	Inhibits angiogenesis and cell survival by targeting HER2 and VEGF, induces apoptosis	(Almatroudi et al., 2023)
13	Baicalein	COX-2, NF-κB, STAT3	Breast, Lung, Liver, Bladder	Inhibits tumor growth and metastasis by downregulating COX-2, NF-κB, and STAT3	(Morshed et al., 2023)
14	Chrysin	ER, AR, COX-2	Prostate, Breast, Lung, Liver	Modulates hormone receptors and inhibits inflammation by targeting COX-2	(Shahbaz et al., 2023)

15	Gallic Acid	p53, Bcl-2, NF-κB	Lung, Colon, Prostate, Esophageal	Induces apoptosis and inhibits cell proliferation by modulating p53 and Bcl-2	(Jiang et al., 2022)
16	Fisetin	p53, NF-κB, PI3K/AKT	Breast, Colon, Prostate, Lung	Induces apoptosis and cell cycle arrest by modulating p53, NF-κB, and PI3K/AKT pathways	Khan et al., 2008
17	Diosgenin	NF-κB, p53, COX-2	Breast, Prostate, Leukemia, Colon	Induces apoptosis and inhibits inflammation by targeting NF-κB, p53, and COX-2	(Sethi et al., 2018)
18	Silibinin	EGFR, STAT3, PI3K/AKT	Prostate, Breast, Lung, Colon	Inhibits cell growth and induces apoptosis by targeting EGFR, STAT3, and PI3K/AKT pathways	(Li et al., 2010)
19	Capsaicin	NF-κB, COX-2, TRPV1	Colon, Breast, Prostate, Pancreatic	Induces apoptosis and inhibits inflammation by modulating NF-κB and COX-2, activates TRPV1 receptors	(Jaganathan et al., 2020)
20	Hesperidin	p53, NF-κB, PI3K/AKT	Breast, Colon, Liver, Leukemia	Induces apoptosis and cell cycle arrest by modulating p53, NF-κB, and PI3K/AKT pathways	(de Oliveira et al., 2020)
21	Rutin	p53, Bcl-2, NF-κB	Colon, Breast, Prostate, Liver	Induces apoptosis by activating p53, Bcl-2 and NF-κB	(Nouri et al., 2020)
22	Naringenin	ER, AR, p53	Breast, Prostate, Colon, Lung	Induces apoptosis by activating p53	(Rauf et al., 2022)
23	Betulinic Acid	p53, Bcl-2, NF-κB	Melanoma, Prostate, Breast, Lung	Induces apoptosis by modulating p53, Bcl-2 and NF-κB	(Banerjee et al., 2024)
24	Ursolic Acid	NF-κB, COX-2, p53	Breast, Colon, Lung, Liver	Inhibits inflammation and induces apoptosis by targeting NF-κB, COX-2, and p53	(Shanmugam et al., 2013)
25	Gingerol	NF-κB, COX-2, TRPV1	Colon, Pancreatic, Breast, Lung	Induces apoptosis and inhibits inflammation by modulating NF-κB and COX-2, activates TRPV1 receptors	(Oyagbemi et al., 2010)
26	6-Shogaol	NF-κB, COX-2, p53	Breast, Colon, Lung, Pancreatic	Induces apoptosis and inhibits inflammation by targeting NF-κB, COX-2, and p53	(Jia et al., 2023)

27	Gossypol	Bcl-2, p53, MDM2	Prostate, Breast, Melanoma, Lung	Inhibits cell survival and induces apoptosis by targeting Bcl-2, p53, and MDM2	(Paunovic et al., 2023)
28	Ellagitannins	p53, Bcl-2, COX-2	Prostate, Colon, Breast, Lung	Induces apoptosis and inhibits inflammation by modulating p53, Bcl-2, and COX-2	(Ismail et al., 2016)
29	Piceatannol	SIRT1, NF-κB, PI3K/AKT	Breast, Colon, Prostate, Leukemia	Modulates apoptosis and cell cycle by targeting SIRT1, NF-κB, and PI3K/AKT	(Banik et al., 2020)
30	Allicin	NF-κB, COX-2, p53	Gastric, Breast, Colon, Lung	Inhibits inflammation and induces apoptosis by targeting NF-κB, COX-2, and p53	(Haghi et al., 2017)
31	Linalool	p53, Bcl-2, NF-κB	Liver, Breast, Lung, Ovarian	Induces apoptosis and inhibits cell survival by modulating p53, Bcl-2, and NF-κB	(Pereira et al., 2018)
32	Betulin	p53, Bcl-2, COX-2	Lung, Colon, Breast, Melanoma	Induces apoptosis and inhibits inflammation by modulating p53, Bcl-2, and COX-2	(Tuli et al., 2021)
33	Emodin	NF-κB, COX-2, p53	Liver, Colon, Lung, Breast	Induces apoptosis and inhibits tumor growth by targeting NF-κB, COX-2, and p53	(Shrimali et al., 2013)
34	Oleuropein	p53, Bcl-2, NF-κB	Breast, Colon, Prostate, Lung	Induces apoptosis and inhibits inflammation by modulating p53, Bcl-2, and NF-κB	(Rishmawi et al., 2022)

2.3 Plant Profile

For this study, *Hemidesmus indicus* and *Ichnocarpus frutescens* were selected based on their ethnomedicinal significance, unique phytochemical profile, underexplored status in nanoparticle-based research, and suitability for dual targeting of diabetes and cancer. Both *H. indicus* and *I. frutescens* have a long-standing role in Ayurvedic and Siddha medicine, particularly for treating diabetes, inflammation, and skin disorders (Dwivedi et al., 2019a; FP et al., 2018a; Naidu et al., 2013a; Nandy et al., 2020b; Pandey, 2021a). Their roots are commonly used in traditional formulations and have shown potential in regulating blood glucose and oxidative stress. Moreover, both plants remain largely underexplored, presenting a significant opportunity to investigate novel bioactives that may demonstrate

enhanced therapeutic efficacy. The study also addressed the rising interest in dual-target therapies, as diabetes and cancer share overlapping mechanisms like oxidative stress, chronic inflammation, and dysregulated apoptosis. Both plants showed potential in modulating these shared pathways. Furthermore, *H. indicus* and *I. frutescens* are abundant and ecologically sustainable in tropical India, making them viable for long-term therapeutic development.

2.3.1 *Hemidesmus indicus*

2.3.1.1 Introduction

Hemidesmus indicus (L.) R. Br. Ex Schult, popularly known as Indian Sarsaparilla, is a perennial, slender, prostrate, or semi-erect shrub belonging to the family Apocynaceae (Lakshmi and Rajendra, 2013).

It is characterized by its woody rootstock and numerous thin, wiry, laticiferous branches covered with purple-brown bark (Figure 2.6). The plant's roots, stems, and leaves are all valued, with the roots being the most commonly used part (Moorthy and Kumar, 2021). The roots are notable for their pleasant aroma, slightly bitter taste, and unique camphoraceous fragrance, often referred to as "kapoori" (Boominathan et al., 2018).

The roots of *Hemidesmus indicus* are highly valued in traditional medicine and are commonly used as a dietary supplement and nutraceutical. They serve as a tonic, blood purifier, and flavoring agent, and are integral in the production of syrups and beverages, particularly in the Indian subcontinent (Banerjee and Ganguly, 2014; Pansare et al., 2018). The popular Sariva syrup, sarsaparilla root drink, or nannari sherbet is especially popular in southern India during hot summer days. It persists as an invaluable resource in a wide range of traditional and modern therapeutic applications (Matharu et al., 2010; Rathod et al., 2021).

Figure 2.6: Plant and root of *Hemidesmus indicus* (L.) R. Br. Ex Schult

2.3.1.2 Taxonomical Classification (Nandy et al., 2020c; Swathi et al., 2019a)

The taxonomical classification of *Hemidesmus indicus* is as follows:

Kingdom: Plantae

Subkingdom: Angiosperms

Phylum: Tracheophytes

Class: Magnoliopsida

Order: Gentianales

Family: Apocynaceae

Genus: *Hemidesmus*

Species: *indicus*

Binomial name: *Hemidesmus indicus* (L.) R. Br. ex Schult.

2.3.1.3 Vernacular Name (Aneja et al., 2008; Pandey, 2021b)

English: False Sarsaparilla, Indian Sarsaparilla, and Country Sarsaparilla

Sanskrit: Lata, Nagajihva, Sariva, Sugandha, Shgandhi, Karala, Krishodari, Dhavalasariva

Hindi: Magrabu, Hindisalsa

Gujarati: Anantvel, Upalsari

Marathi: Upalsan

Oriya: Onotomulo, Suguddimalo

Tamil: Nannari

Telugu: Sugandhipala

Persian: Ushba

2.3.1.4 Origin and Geographical Distribution

Hemidesmus indicus, native to India, grows in a variety of habitats ranging from mesophytic to semi-dry conditions. It is found in the lowlands and at altitudes up to 600 meters (Sena et al., 2023). The plant grows widely in central, western, and southern India, as well as from the upper Gangetic plain eastward to West Bengal and Assam. Common habitats of *Hemidesmus indicus* include hedges, degraded areas, scrub jungles, moist deciduous forests, and uncultivated soils. (Nandy et al., 2020c). *Hemidesmus indicus* is mostly native to India, although it is also found in Bangladesh, Pakistan, Iran, Malaysia, Indonesia, Sri Lanka, and the Moluccan Islands. This widespread distribution highlights the plant's adaptability to diverse environmental conditions across South and Southeast Asia (Kher et al., 2020).

2.3.1.5 Botanical Distribution

Hemidesmus indicus is a branching shrub characterized by its opposite leaves and sub-sessile flowers arranged in lateral umbels. The rhizome of the plant is woody, and it is typically found in open scrub jungles, hedges, and uncultivated land. This slender, laticiferous, twining, perennial shrub grows rapidly and exhibits tuberous, woody, and aromatic roots (Yazhni et al., 2021). The plant is known as "Anantmool," meaning "the eternal root," due to its extensive root system that spreads long distances underground (Chakrabortty and Choudhary, 2014). The stems are terete, slender, and narrow; they produce milky latex and are thickened at the nodes. *Hemidesmus indicus* has thinner, frequently variegated lower leaves with white lines on the upper surface, and larger, dark green upper leaves without variegation. Each flower comprises five lobes on the calyx, five stamens, a tubular gamopetalous corolla that is about 5–6 mm long, and a bicarpellary pistil, free ovaries with numerous ovules (Misra and Saema, 2016). *Hemidesmus indicus* produces terete, paired, thin, wildly distinct follicles that eventually compress to a length of 10–15 cm. It yielded a number of seeds characterized by flattened, oblong, ventrally ridged, black, with microscopic silvery-white hairs (Purohit et al., 2014).

2.3.1.6 Traditional Use

Hemidesmus indicus is a well-known traditional medicinal herb extensively used in the Unani, Siddha, and Ayurveda systems of medicine. Its root has long been used as a treatment for a variety of illnesses, such as skin conditions, infections, diarrhea, dysentery, Diabetes, nephritic symptoms, menorrhagia, postpartum recuperation, and stomach aches (Pandey, 2021b). Table 2.4 compiles the traditional uses of *H. indicus*, including the parts used and diseases treated. In addition to treating these conditions, *Hemidesmus indicus* is also valued for its properties as a blood purifier, body coolant, and appetite stimulant. It is commonly used to promote overall health and vitality (Manjulatha et al., 2014;

Shilpha et al., 2022). One notable herbal formulation, Vembadamennai, is administered orally for the treatment of ulcers (Sena et al., 2023). In Sri Lanka, traditional healers use a decoction containing *Nigella sativa* seeds, *Hemidesmus indicus* root bark, and *Smilax glabra* rhizome to treat cancer (Iddamaldeniya et al., 2006).

Table 2.4: Traditional uses of *Hemidesmus indicus* based on the different plant parts used

Plant Part	Ethnomedicinal Use	References
Root	Blood purifier, Diarrhea, dysentery, skin disease, Snakebite, Sore of eczema, Diabetes, Stomach pain, urinary tract disorders, Fever, Cough and cold in children, Gonorrhea, Toothache, feet infection, Stomach pain, anemia, leucorrhea, Stomach ulcer, bronchitis, Jaundice, Retention of the placenta, Lactation, nervous disorder	(Alam et al., 1994)
Aerial parts	Jaundice	(Bandara et al., 2023)
Root bark	Stomach disorder, blood purifier	(Kawlni et al., 2017)
Rhizome	Reduces abdominal pain	(Moorthy and Kumar, 2021)
Tuber	Abdominal colic	(Darshini et al., 2024)
Root and Leaf	Stomach disorder	(Vishali et al., 2011)
Leaf	Jaundice, Diuretics, Chronic cough, diarrhea, Diabetes, Eczema	(Pansare et al., 2018)
Stem	Headache, cough, and cold	(Rajput, 2022)
Whole Plant	Hair growth, Stomach pain, Cooling agent, pain killer, Hypertension, Anemia, leukoderma, Fever, Menstrual disorder, psoriasis, rheumatism	(Manjulatha et al., 2014)

2.3.1.7 Phytochemistry

Hemidesmus indicus, is renowned for its diverse and rich phytochemical profile. It contains several bioactive compounds, including Alkaloids, phenolic substances, lignin, inulin, terpenoids, flavonoids, alkaloids, tannins, and cardiac glycosides. The roots of *Hemidesmus indicus* are particularly rich in therapeutic phytocompounds (Balaji et al., 2017). Notable constituents include hemidesmol, resin, glucoside, tannins, and resin acid. Additionally, compounds such as lupeol, β-sitosterol, α- and β-amyrins, lupeol acetate, β-amyrin acetate, and hexa-tricontane acid are present (Subramaniyan, 2019). The roots also contain significant amounts of 2-hydroxy-4-methoxy benzaldehyde, along with

steroids, terpenoids, flavonoids, and saponins (Kharat and Mokat, 2020). An important component is the crystalline material, which makes up 80% glucose hemidesmol, glucoside, resin acid, and sterol. The stem contains glycosides such as hemidine and indicine. Furthermore, extracts of the stem in chloroform and alcohol yield two pregnane glycosides: hemidescine and emidine. These glycosides contribute to the plant's medicinal properties, enhancing its therapeutic potential (Chandra et al., 1994; Das et al., 2017). Leaves of *Hemidesmus indicus* are known for their tannin content, which represents 2.5% of the leaf composition. The leaves also contain coumarin lignoids, including hemidesminine, hemidesmin 1, and hemidesmin 2 (Swathi et al., 2019a). The flowers contain glycosides and flavonoids such as hyperoxide, isoquercetin, and rutin (Aneja et al., 2008).

2.3.1.8 Pharmacological activity

Hemidesmus indicus is renowned for its extensive pharmacological activities (Baheti et al., 2006; Das and Singh Bisht, 2013; Ferruzzi et al., 2013; Mehta et al., 2012; Nandy et al., 2020a; Saritha et al., 2015) and a comprehensive overview of these properties is provided in Table 2.5.

Table 2.5: Pharmacological activity of chemical constituents of *Hemidesmus indicus*.

Plant Part	Chemical Constituent	Chemical Formula	Pharmacological Activity
Root	2-hydroxy-4-methoxybenzaldehyde (MBALD)	$C_8H_8O_3$	Antioxidant, Antimicrobial, Anti-inflammatory
Root	Limonene	$C_{10}H_{16}$	Antioxidant, anti-inflammatory, Anticancer, Antimicrobial, Digestive aid
Root	Methyl salicylate	$C_8H_8O_3$	Analgesic, Anti-inflammatory, Antimicrobial
Root	Borneol	$C_{10}H_{18}O$	Analgesic, Anti-inflammatory, Antimicrobial, Sedative, Neuroprotective
Root	Hydroquinone	$C_6H_6O_2$	Antioxidant, Depigmenting agent
Root	4-hydroxy-3-methoxy benzaldehyde (vanillin)	$C_8H_8O_3$	Antioxidant, Anti-inflammatory, Antimicrobial, Flavoring agent
Root	α-muurolol	$C_{15}H_{26}O$	Antimicrobial, anti-inflammatory
Root	(E)-nerolidol	$C_{15}H_{26}O$	Antimicrobial, Anti-inflammatory,

			Sedative, Skin penetration enhancer
Root	α-bisabolol	$C_{15}H_{26}O$	Anti-inflammatory, Antimicrobial, Skin healing, Antioxidant
Root	Amyl cinnamate	$C_{14}H_{18}O_2$	Antimicrobial, UV protection, Fragrance, Antioxidant
Root	Ledol	$C_{15}H_{26}O$	Anti-inflammatory, Antimicrobial, Sedative
Root	Nerolidol	$C_{15}H_{26}O$	Antimicrobial, Anti-inflammatory, Sedative, Skin penetration enhancer
Root	Borneol	$C_{10}H_{18}O$	Analgesic, Anti-inflammatory, Antimicrobial, Sedative, Neuroprotective
Root	α-terpinyl acetate	$C_{12}H_{20}O_2$	Antimicrobial, Anti-inflammatory, fragrance agent
Root	1,8-cineol (eucalyptol)	$C_{10}H_{18}O$	Decongestant, Expectorant, Anti-inflammatory, Antimicrobial, Analgesic
Root	Hemidesmosides A-C	$C_{45}H_{72}O_{16}$	Antioxidant, Antimicrobial, Anti-inflammatory, Immunomodulatory
Root	Plocoside A	$C_{41}H_{68}O_{12}$	Anticancer, Antioxidant, Antimicrobial
Root	Oleanenes	$C_{30}H_{48}O_2$	Antioxidant, Anti-inflammatory, Anticancer
Root	Ursenes	$C_{30}H_{48}O_2$	Antioxidant, Anti-inflammatory, anticancer
Root	Lupene	$C_{30}H_{50}O$	Antioxidant, Anti-inflammatory, Anticancer
Root	β-amyrin acetate	$C_{32}H_{52}O_2$	Anti-inflammatory, Hepatoprotective, Antimicrobial, Analgesic
Root	β-sitosterol	$C_{29}H_{50}O$	Anti-inflammatory, Cholesterol-lowering, Anticancer, Immunomodulatory
Root	Lupeol acetate	$C_{32}H_{52}O_2$	Anti-inflammatory, Hepatoprotective, Anticancer, Antimicrobial
Root	Hemidesmine (coumarinolignoid/lignans)	$C_{20}H_{18}O_4$	Anti-inflammatory, Immunomodulatory, Antioxidant, Anticancer
Root, leaves	Hemidesmin-1 and 2 (coumarinolignoids)	$C_{20}H_{18}O_4$	Antioxidant, Anticancer Anti-inflammatory, Immunomodulatory
Root	Hemidesmus ester	$C_{23}H_{38}O_2$	Anti-inflammatory Antioxidant, Antimicrobial
Stem	Hindicusine	$C_{21}H_{32}O_8$	Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer, Cardioprotective
Stem	Di-O-acetylhindicusine (pregnane glycoside)	$C_{25}H_{36}O_{10}$	Antioxidant, Antimicrobial, Anti-inflammatory, Immunomodulatory
Stem	Denicunine	$C_{27}H_{42}O_8$	Neuroprotective, Anticancer, Anti-inflammatory
Stem	Heminine (pregnane glycoside)	$C_{25}H_{36}O_{10}$	Cardioprotective, Anti-inflammatory, Anticancer
Stem	Desinine	$C_{27}H_{42}O_8$	Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer, Neuroprotective
Stem	Indicine	$C_{24}H_{38}O_7$	Antioxidant, Antimicrobial, Anti-inflammatory, Anticancer
Stem	Hemidine	$C_{22}H_{36}O_7$	Antioxidant, Anticancer, Cardioprotective
Stem	Indicusin	$C_{25}H_{36}O_{10}$	Anti-inflammatory, Antioxidant, Anticancer

Stem	Hemidescine	$C_{25}H_{36}O_{10}$	Anticancer, Anti-inflammatory, Antioxidant
Stem	Emidine	$C_{24}H_{38}O_8$	Antioxidant, Neuroprotective, Anti-inflammatory
Stem	Medidesmine	$C_{21}H_{32}O_8$	Cardioprotective, Antioxidant, Anticancer
Stem	Hemisine	$C_{22}H_{36}O_7$	Anticancer, Anti-inflammatory, Antioxidant
Stem	Demicine	$C_{27}H_{42}O_8$	Neuroprotective, Antioxidant, Anti-inflammatory
Leaves, Flower	Quercetin	$C_{15}H_{10}O_7$	Antioxidant, Anti-inflammatory, Cardiovascular health, Anticancer, Antiviral, Antimicrobial, Allergy relief
Flower	Hyperoside	$C_{21}H_{20}O_{12}$	Antioxidant, Neuroprotective, Cardioprotective, Anticancer, Anti-inflammatory
Flower	Isoquercetin	$C_{21}H_{20}O_{12}$	Antioxidant, Anti-inflammatory, Cardiovascular health, Anticancer, Antidiabetic, Antiviral
Flower	Rutin	$C_{27}H_{30}O_{16}$	Antioxidant, Vascular health, Anti-inflammatory, Antiallergic, Anticancer, Neuroprotective, Antidiabetic

2.3.2 *Ichnocarpus frutescens*

2.3.2.1 Introduction

Ichnocarpus frutescens R. Br., commonly known as Krishna Sariva, is a red, woody climber with slender branches and a characteristic rusty red appearance, as shown in Figure 2.7 (FP et al., 2018b). This evergreen, laticiferous climbing shrub is found throughout India and is also known by other common names such as black creeper, Palvalli, and Parvalli (Rout et al., 2019). *Ichnocarpus frutescens* holds significant importance in traditional Indian medicine, where it is used to treat a wide range of ailments, including Diabetes, dysentery, cholera, asthma, bronchitis, coughs, dog bites, snake bites, sores, syphilis, night blindness, smallpox, fever, jaundice, measles, and wounds (Dwivedi et al., 2019b). Additionally, it is used to manage fevers, gout, rheumatism, arthritis, epilepsy, venereal diseases, herpes, and various skin conditions (Naidu et al., 2013b). Due to its extensive use in traditional medicine, there is growing interest in the study of *Ichnocarpus frutescens* to identify its phytochemical constituents and therapeutic potential and ensure its non-toxicity.

Figure 2.7: Stem, Leaves and Root of *Ichnocarpus frutescens* R. Br.

2.3.2.2 Taxonomical Classification (Kumarappan et al., 2015a; Mohsina et al., 2022)

Kingdom: Plantae

Subkingdom: Viridaeplantae

Phylum: Magnoliophyta

Class: Magnoliopsida

Subclass: Magnoliidae

Order: Gentianales

Family: Apocynaceae

Genus: *Ichnocarpus*

Species: *frutescens*

Binomial name: *Ichnocarpus frutescens* (L.) W. T. Aiton.

2.3.2.3 Vernacular Name (Prathib et al., 2017; Singh and Singh, 2012)

Hindi : Kali-dudhi, Siamalata, Krishna sariva

English: Black creeper

Marathi: Krishnssariva, Kantebhouri

Malyali : Paralvally

Telgu: Illukatte, Nalateage

Sanskrit : Syamalata, Sariva, Paravalli, Krishna

Bengali : Dudhi, Syamalota

Tamil : Paravalli, Udargodi

Deradhun : Bel kamu

Assamese: Lamkandol, Paharukihandan

Kannada : Karehambu, Gorwiballi

2.3.2.4 Geographical Distribution

Ichnocarpus frutescens is a large, evergreen woody creeper widely distributed across tropical and subtropical regions of Asia and parts of Australia (Singh and Singh, 2012) In India, it is commonly found throughout the country, particularly in states like Rajasthan, Tamil Nadu, Karnataka, and Madhya Pradesh. The plant is also present in the Himalayan region, ascending to altitudes of up to 1,200 meters (Chaudhary et al., 2012). It thrives in various habitats, such as forests, scrublands, and along roadsides. Beyond India, *Ichnocarpus frutescens* is found in Nepal, Bangladesh, and Sri Lanka, adapting well to both lowland and upland areas. In Southeast Asia, the plant grows in countries such as Thailand, Malaysia, and Indonesia, where it is commonly found in open forests, secondary forests, and coastal areas. The plant is also present in China and the Philippines,

typically thriving in moist, shaded environments. Additionally, *Ichnocarpus frutescens* is found in Java, and extends to northern Australia, demonstrating its ecological versatility (Nirala et al., 2024).

2.3.2.5 Botanical Description

The plant is characterized by its evergreen leaves, which are simple, opposite, and alternate in arrangement. The leaves have an entire margin with pinnate venation and 5-7 pairs of main nerves, exhibiting finely reticulate venation. They are elliptic-oblong to broadly lanceolate in shape, with an acute or acuminate apex. The petiole of the leaves measures between 3-6 mm in length, and the leaves are exstipulate (Kharat and , Shylaja.H , G.L.Viswanatha, 2010a). The stem of the plant is woody and cylindrical, showing herbaceous branching, and it is a climbing type. The surface of the stem is rough and covered with hairs. When the stem is injured or incised, it exudes a creamy white latex. The root system of the plant is a tap root, which is cylindrical, considerably long, and measures 1-5 cm in diameter. The roots are dark or dusty brown and crookedly twisted. They have slight transverse cracks at the bends and tiny longitudinal creases all over their surface (Singh and Singh, 2012). The flowers of the plant are small, fragrant, and either white or greenish-white. The inflorescence is pedunculate cymose. The calyx consists of 5 sepals that are gamopetalous, with ovate and acute lobes that are covered in fulvous hairs. The corolla is made up of 5 gamopetalous petals, with the corolla tube measuring 2.5-3.0 mm in length (Mammen et al., 2011). The lower portion of the tube is narrow, while the middle part is inflated and almost globular, encasing the stamens. The upper part is glandular with white hairs on the upper side and restricted under the 5 mm long lobes. The ovary is one-celled with parietal placentation and contains many ovules. The fruit is a pair of cylindrical follicles, measuring 10-15 cm in length and 4 mm in width, which are straight or slightly curved. The seeds are black, linear, and range from

1.3-2 cm in length. They are not beaked but have a scanty white coma, a tuft of silky hair at one end that is as long as the seed. The plant flowers and bears fruit from September to December and again from January to April. It thrives in full sunlight and well-drained soil. Propagation can occur through seeds or vegetative methods (Mohsina et al., 2022).

2.3.2.6 Traditional Use

Ichnocarpus frutescens is traditionally used to treat various health conditions, including atrophy, seizures, coughing, delirium, diarrhea, measles, splenomegaly, TB, and tumors of the abdomen and glands The plant is widely employed in indigenous medicine to manage Herpes, rheumatism, arthritis, fever, gout, epilepsy, and skin conditions. The roots specifically relieve rheumatic pain and are used as a blood purifier (Kumarappan et al., 2015b). In some traditional practices, the roots are used to treat jaundice and are combined with other plant roots to address stomach cancer (Deepak K Dash et al., 2007; Dwivedi et al., 2019b).

Ichnocarpus frutescens is also valued for its use in promoting milk production, with dried root powder being taken as a lactagogue (Bhandary et al., 1995). In some tribal communities, the roots and flowers are used to manage diabetes, and the leaves are applied to cuts to stop bleeding (Prathib et al., 2017). Table 2.6 compiles the traditional uses of *Ichnocarpus frutescens*, including the parts used and diseases treated. These applications highlight the diverse and significant role of *Ichnocarpus frutescens* in traditional medicine.

Table 2.6: Traditional uses of *Ichnocarpus frutescens* based on the different plant parts used

Plant Part	Traditional Use	References
Leaves	Decoction used for fever, diabetes, and skin eruptions	(Singh and Singh, 2012)
	Used to treat fever	(Khatun et al., 2013)
	Used for fever, cramps, night blindness, and headache.	(Vaishnaw et al., 2023)
	Leaves are used to stop bleeding from cuts.	(Singh and Singh, 2012)

	Leaf extract is used for stomach pain.	(Srujana et al., 2018)
	Boiled leaves in oil relief from wounds between fingers.	(Pandurangan et al., 2008)
Aerial Part	Treat skin eruptions	(Girthie et al., 2022)
Stem	Treat fever and skin eruptions.	(Meher, 2013)
	Treat redness of the eye.	(Naidu et al., 2013b)
Roots	Used as tonic	(Prathib et al., 2017)
	Decoction used as antidote for snakebite; dose: 5-10 ml every 1-2 hours.	(Kumar and Gairola, 2020)
	Decoction is used as a blood purifier	(Kumar Singh and Pratap Singh, 2014)
	Used to treat Jaundice	(Nirala et al., 2024)
	Dried root powder used as lactogogue	(Singh and Singh, 2012)
	Roots are used as diuretic and diaphoretic.	(Patil et al., 2015)
	Used in fever, blood purifier, diabetic	(Kumarappan et al., 2015a)
Flowers	Used to cure diabetes.	(Deepak K Dash et al., 2007)
Latex	Used to treat skin infections.	(Anbarashan and Padmavathy, 2010)
Whole Plant	Used for bleeding gums, cough, dysentery, haematuria, measles, night blindness, anorexia, leucorrhoea, syphilis, urinary calculi, rheumatism, bone fractures, skin infections, diabetes, and liver disorders.	(Mohsina et al., 2022)

2.3.2.7 Phytochemistry

Ichnocarpus frutescens is a plant known for its diverse range of phytochemical compounds, which are distributed across various parts of the plant, including the leaves, flowers, stems, and roots. Each part of the plant contains specific compounds that contribute to its overall chemical profile and potential pharmacological properties. The leaves of *Ichnocarpus frutescens* are rich in flavonoids and phenolic compounds. Notable flavonoids present in the leaves include apigenin, luteolin, kaempferol, and its derivative kaempferol-3-galactosid (Aggarwal et al., 2010). Additionally, quercetin, a well-known antioxidant, is also found in the leaves. Apart from flavonoids, the leaves contain ursolic acid acetate, a triterpenoid, as well as several phenolic acids such as Sinapic acid, protocatechuic acid, syringic acid, and vanillic acid (Pandurangan et al., 2010). The flowers primarily contain flavonoids, with quercetin and its glycoside form, quercetin-3-O-β-D-glucopyranoside, being the major compounds. The stems of *Ichnocarpus*

frutescens are a rich source of triterpenoids and other unique compounds. Key triterpenoids found in the stems include α-amyrin, lupeol, α-amyrin acetates, lupeol acetates, friedelin, and epi-friedelinol (Srujana et al., 2018). The presence of β-sitosterol, a phytosterol, adds to the stem's bioactive profile. In addition to these, the stems contain compounds like β-L-sarbopyranoside, 6,8,8-trimethylpentacosan-7-one, Benzocosanyl arachidate, n-butyl oleate, n-octyl tetracontane, tetratriacontadiene, and n-nonadecanyl benzoate (Aggarwal et al., 2011; FP et al., 2018b) These diverse compounds contribute to the broad range of biological activities associated with the plant. The roots are primarily noted for containing ursolic acid, a triterpenoid compound. In summary, *Ichnocarpus frutescens* exhibits a complex phytochemical profile, with each plant part containing specific compounds that contribute to its traditional medicinal uses.

2.3.2.8 Pharmacological activity

Ichnocarpus frutescens is known for its broad range of pharmacological activities, owing to its rich phytochemical composition. It*s* pharmacological activities include antioxidant, anti-inflammatory, anticancer, hepatoprotective, antimicrobial, antidiabetic, cardioprotective, neuroprotective, anti-allergic, and wound-healing effects (D K Dash et al., 2007; Kharat and , Shylaja.H , G.L.Viswanatha, 2010b; Malathy N S, 2009; Pandurangan et al., 2009). These activities highlight its potential use in traditional medicine and modern therapeutic applications. A comprehensive overview of these properties is provided in Table 2.7.

Table 2.7: The pharmacological activity of chemical constituents of *Ichnocarpus frutescens*

Plant Part	Chemical Constituent	Chemical Formula	Pharmacological Activity
Leaves	Apigenin	$C_{15}H_{10}O_5$	Antioxidant, anti-inflammatory, Neuroprotective, anxiolytic, cardioprotective, skin protective
Leaves	Luteolin	$C_{15}H_{10}O_6$	Antioxidant, anticancer, cardioprotective, antiviral, anti-allergic
Leaves	Kaempferol	$C_{15}H_{10}O_6$	Antioxidant, anticancer, Neuroprotective, cardioprotective, estrogenic activity, antimicrobial
Leaves	Kaempferol-3-galactoside	$C_{21}H_{20}O_{11}$	Antioxidant, anti-inflammatory, Cardioprotective, anticancer
Leaves	Quercetin	$C_{15}H_{10}O_7$	Antioxidant, anti-inflammatory, anticancer, Cardioprotective, antiviral, neuroprotective, antihypertensive
Leaves	Ursolic acid acetate	$C_{32}H_{50}O_4$	Anti-inflammatory, anticancer, Antimicrobial, hepatoprotective, skin protective
Leaves	Vanillic acid	$C_8H_8O_4$	Antioxidant, antimicrobial, Antidiabetic, anti-inflammatory, neuroprotective
Leaves	Protocatechuic acid	$C_7H_6O_4$	Antioxidant, antimicrobial, Anti-inflammatory, anti-cancer, cardioprotective
Flowers	Quercetin	$C_{15}H_{10}O_7$	Antioxidant, anti-inflammatory, anticancer, Cardioprotective, antiviral, neuroprotective, antihypertensive
Flowers	Quercetin-3-O-β-D-glucopyranoside	$C_{21}H_{20}O_{12}$	Antioxidant, anti-inflammatory, Anticancer, cardioprotective
Stems	α-Amyrin	$C_{30}H_{50}O$	Anti-inflammatory, hepatoprotective, Analgesic, antimicrobial, antiparasitic
Stems	Lupeol	$C_{30}H_{50}O$	Anti-inflammatory, anticancer, Antimicrobial, hepatoprotective, skin protective, anti-arthritic
Stems	α-Amyrin acetates	$C_{32}H_{52}O_2$	Anti-inflammatory, Hepatoprotective, antimicrobial
Stems	Lupeol acetates	$C_{32}H_{52}O_2$	Anti-inflammatory, anticancer, Antimicrobial, skin protective, anti-arthritic
Stems	β-Sitosterol	$C_{29}H_{50}O$	Cholesterol-lowering, anti-inflammatory, Anticancer, immunomodulatory, antioxidant, prostate health
Stems	β-L-sarbopyranoside	$C_{12}H_{22}O_{11}$	Antioxidant, antimicrobial, Antidiabetic, cardioprotective
Stems	6,8,8-Trimethylpentacosan-7-one	$C_{28}H_{56}O$	Potential for exploring anti-inflammatory and antimicrobial effects
Stems	n-Butyl oleate	$C_{22}H_{42}O_2$	Emollient, antimicrobial, Potential skin protective, anti-inflammatory
Stems	n-Octyl tetracontane	$C_{48}H_{98}$	Potential bioactive roles to be explored, possibly in skincare or antimicrobial applications
Stems	Tetratriacontadiene	$C_{34}H_{66}$	Potential bioactive roles to be explored, possibly anti-inflammatory or antioxidant
Stems	n-Nonadecanyl benzoate	$C_{26}H_{44}O_2$	Potential roles in skin protection, emollient properties
Stems	Benzocosanyl arachidate	$C_{48}H_{92}O_2$	Potential bioactive roles in anti-inflammatory or antimicrobial applications
Roots	Ursolic acid	$C_{30}H_{48}O_3$	Anti-inflammatory, anticancer, hepatoprotective, Antimicrobial, anti-diabetic, cardioprotective, skin protective, anti-ulcer