Phytochemical and Pharmacological Evaluation of *D. malabarica* and *Anacyclus pyrethrum*: A Review

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ABSTRACT:
Traditional medicine has made extensive use of species from the *Diospyros L.* genus (Ebenaceae family) to cure a variety of illnesses, particularly infectious ones. To date, Diospyros species have yielded active main chemicals that have been identified and pharmacologically verified, including triterpenoids, tannins, and naphthoquinones. In Morocco and Algeria, *Anacyclus pyrethrum* (L.) (Asteraceae) is a common annual medicinal herb. The majority of its components are utilized in traditional medicine, with the roots being the most crucial. The current study provides an overview of the most recent data about its pharmacological and phytochemical characteristics. Among other medicinal properties, the current study notes that *D. malabarica* and *Anacyclus pyrethrum* have antidiabetic, antioxidant, and anti-inflammatory properties.

INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic disorder characterized by persistent hyperglycemia, which occurs due to either insufficient insulin secretion from pancreatic β-cells or the body's inability to effectively utilize insulin. The prevalence of DM is a significant public health issue, affecting more than 400 million people globally. This condition progressively leads to severe complications, including microvascular, macrovascular, and neuropathic damage, all of which can be life-threatening. The rise in diabetes cases worldwide is largely attributed to sedentary lifestyles, with projections estimating that by 2030, approximately 366 million individuals, particularly those aged 65 and above, will be affected (Khursheed et al., 2019).

The complications of DM are extensive, affecting multiple organ systems. These include diabetic nephropathy, neuropathy, retinopathy, cardiovascular diseases, and susceptibility to various infections. Diabetes is broadly categorized into two main types: type 1 and type 2. Type 1 diabetes is an autoimmune disorder where the immune system attacks pancreatic β-cells, leading to reduced or complete loss of insulin production. In contrast, type 2 diabetes arises from insulin resistance or dysfunction of β-cells, which hinders the body's ability to utilize insulin effectively.

The pharmacological management of hyperglycemia in DM involves several classes of medications. Sulfonylureas stimulate insulin release from pancreatic β-cells, biguanides reduce hepatic glucose production, peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists enhance insulin sensitivity, and α-glucosidase inhibitors slow down carbohydrate absorption in the intestines. These medications can be administered as monotherapy or in combination with other hypoglycemic agents. However, the use of these conventional drugs is associated with significant drawbacks, including the risk of severe hypoglycemia, weight gain, low drug potency, and unpredictable side effects caused by altered drug metabolism. Additional issues include poor target specificity, limited solubility, and permeability challenges. Despite advancements in anti-hyperglycemic therapies, managing diabetes effectively remains a challenge. The primary focus of diabetes treatment is to minimize the long-term complications of the disease and develop more effective and balanced therapies that maintain optimal

glucose levels. Addressing these challenges requires continuous improvement in treatment strategies to ensure better glycemic control and overall patient well-being (Wong et al., 2017).

1.1. Epidemiology of Diabetes mellitus

Epidemiology plays a crucial role in understanding and managing diabetes by providing insights into disease burden, prevalence trends, and risk factors. Epidemiological studies facilitate the identification of patterns and shifts in diabetes occurrence. Additionally, large-scale studies uncover risk factors that contribute to the disease's pathophysiology. These studies consider a range of influences, such as genetics, lifestyle, dietary habits, and environmental conditions.

Type 1 diabetes, an autoimmune disorder primarily affecting children and young adults, accounts for about 10% of all diabetes cases globally. In contrast, type 2 diabetes, which affects 90–95% of people with diabetes, is more common among adults and is linked to insulin resistance. The global prevalence of diabetes has been on a sharp rise. In 2000, approximately 2.8% of the world's population was affected by diabetes, a figure projected to increase to 4.4% by 2030. This alarming rise is driven by sedentary lifestyles, unhealthy diets, and an aging global population.

In the United States, diabetes affects a significant portion of the population. According to the January 2011 National Diabetes Fact Sheet, 25.8 million people, accounting for 8.3% of the U.S. population, were diagnosed with diabetes. Of these, 1.9 million new cases were reported among adults aged 20 and above. The prevalence rates for men and women stood at 11.8% and 10.8%, respectively. Global estimates predict that the total number of diabetes cases could double within 20 years, reaching 180 million.

The prevalence of diabetes varies across countries and economic regions. In wealthier nations, diabetes is more common among individuals aged 60 and above, whereas in developing countries, it affects people aged 40 to 60. By 2030, diabetes prevalence is expected to increase by 54%, reflecting an annual growth rate of 2.2%, nearly double the global population growth rate. Alarmingly, China and India are projected to have the highest diabetes burden, with a combined total of approximately 154 million affected individuals.

The prevalence of diabetes also differs across regions and population groups. For example, the prevalence rate among the Indian diaspora (2.2%) is higher than that of European populations (1.2%). Within India, southern states like Tamil Nadu report a higher prevalence (10.4%) compared to Maharashtra (8.4%) and Jharkhand (5.3%). Regionally, diabetes prevalence rates vary from 12.1% in North America to 8.1% in Europe, 4% in Africa, and 1% in Asia.

Multiple logistic regression analyses have identified several key risk factors for diabetes. Age, male sex, urban residence, family history of diabetes, hypertension, abdominal and generalized obesity, and socioeconomic status have all been significantly associated with an increased risk of developing diabetes. Additionally, similar risk factors, including age, family history, obesity, hypertension, and socioeconomic status, have been linked to the development of prediabetes (Wild et al., 2004).

1.2. Classification of diabetes

Diabetes mellitus is broadly classified into two primary types: type 1 and type 2 diabetes. Type 1 diabetes, also known as juvenile diabetes, is characterized by a severe deficiency of insulin due to the autoimmune destruction of pancreatic β-cells. In contrast, type 2 diabetes is marked by insulin resistance combined with inadequate insulin production. Type 1 diabetes accounts for approximately 5–10% of the global diabetic population, making it significantly less common than type 2 diabetes. The autoimmune nature of type 1 diabetes is evidenced by the presence of specific autoantibodies. These include islet cell autoantibodies, insulin autoantibodies, glutamic acid decarboxylase (GAD) autoantibodies, and autoantibodies targeting tyrosine phosphatase proteins IA-2α and IA-2β. These autoantibodies serve as biomarkers indicating immune-mediated destruction of pancreatic β-cells. Additionally, genetic predisposition plays a vital role in the development of type 1 diabetes. The condition is strongly associated with the Human Leukocyte Antigen (HLA) system, particularly the DQA and DQB gene variants, which are key genetic contributors to disease susceptibility.

Each person with type 1 diabetes has a variable rate of β cell distraction. Children and newborns showed rapid cell death, whereas adults showed gradual cell death. Compared to hyperglycemia, ketoacidosis was the initial sign of the illness in children and adolescents. Others had

mild hyperglycemia when fasting, which quickly progresses to severe hyperglycemia and ketoacidosis. There is no known because for certain type 1 diabetics, who have persistent insulinopenia, are at risk for ketoacidosis, and show no signs of autoimmunity, all of which are characteristics of idiopathic diabetes. Multiple genetic predispositions and poorly defined environmental variables contribute to the autoimmune damage of diabetes. Additionally, these people are at risk for developing other autoimmune diseases (Mayorov et al., 2011).

1.3. Type 2 Diabetes

Insulin resistance and a relative lack of insulin production are characteristics of type 2 diabetes. The majority of people with type 2 diabetes are fat, and insulin resistance is a result of obesity. The exact aetiology of this kind of diabetes is unknown, and there is no indication of autoimmune distraction in the β cells. One of the factors contributing to the development of type 2 diabetes is an elevated proportion of body fat, which is mostly distributed in the abdominal area, in individuals who are not obese. Because hyperglycemia develops slowly and is typically recognized after additional issues have occurred, this kind of diabetes is often not diagnosed for a long time.Type 2 diabetes is more prevalent across all ethnic groups and has a strong hereditary component. Nevertheless, the disease's genetic makeup is more nuanced and unclear: The development of diabetes mellitus involves multiple interconnected physiological dysfunctions, which contribute to abnormal glucose metabolism. These key mechanisms include: a) Reduced Insulin Secretion: The β-cells of the islets of Langerhans in the pancreas produce insufficient amounts of insulin, leading to impaired glucose uptake by cells. b) Excessive Glucagon Release: The α-cells of the pancreatic islets secrete an abnormally high amount of glucagon, promoting increased blood glucose levels. c) Enhanced Hepatic Glucose Production: The liver increases gluconeogenesis and glycogenolysis, resulting in elevated glucose release into the bloodstream. d) Neurotransmitter Imbalance and Insulin Resistance in the Brain: Disruption of brain neurotransmitter signaling reduces the body's ability to regulate glucose and contributes to insulin resistance. e) Increased Fat Breakdown (Lipolysis): Excessive lipolysis releases free fatty acids into the bloodstream, which further exacerbates insulin resistance. f) Elevated Renal Glucose Reabsorption: The kidneys increase the reabsorption of glucose, which prevents its excretion in urine, leading to higher blood glucose levels. g) Reduced Incretin Response: The small intestine shows a diminished incretin effect, thereby decreasing insulin secretion in response to meals. h) Impaired Glucose Uptake in Peripheral Tissues: Skeletal muscle, liver, and adipose tissue exhibit reduced glucose uptake due to insulin resistance, resulting in hyperglycemia (Ojha et al., 2019).

1.4. Plant Profile

1.4.1. Collection

D. malabarica, a member of the Ebenaceae family, was taken from the villages of Hooghly, West Bengal, India, in June and July 2020. It is known locally as Gaub (Hindi), Gaab (Hindi), and Tinduka (Sanskrit), and in English as Gaub persimmon and Indian persimmon (Samtiya et al., 2021).*Anacyclus pyrethrum*, often known as Akar kara, is a widely spread plant that goes by several names in several nations. About 70% of the world's pyrethrum extract is produced in Kenya, which leads the globe in production. Rwanda, Tanzania, and Tasmania, Australia, are other major producers of pyrethrum. It may be found in Bengal, Jammu & Kashmir, and the Himalayan region of India (Atanasov et al., 2021).

1.4.2. Classification

Kingdome: -	Plantae
Division: -	Spermatophyta
Sub-division: -	Angiosperms
Class: -	Dicotyledons
Sub class: -	Metachlamydae
Order: -	Campanulate
Family: -	Compositae or Asteraceae
Genus: -	Anacyclus
Species: -	Pyrethrum

One of the Asteraceae family's spontaneous plant species, *A. pyrethrum* (L.), is native to Morocco and Algeria (Bellakhdar et al., 1997, Hmamouchi et al., 1999). Both the *A. pyrethrum* var. pyrethrum (L) and the *A. pyrethrum* var. depressus (Ball) Maire are members of this species (Jawhari et al., 2020). Numerous taxonomists have addressed botanical and systematic descriptions of this species in a variety of faedora publications (Jawhari et al., 2021). Research on the chemical and biological activity of the *A. pyrethrum* species has gained more attention in recent years.

The existence of a broad range of phytochemicals, of which around 100 distinct compounds have been reported to far, has been confirmed by a number of previously published investigations on the chemical composition of *A. pyrethrum*(El-Mokhtari et al., 2020, Elazzouzi et al., 2020).The roots of *A. pyrethrum* are used in traditional medicine to cure a variety of conditions, including female infertility, toothaches, angina, salivary secretions, digestive issues, drowsiness, and even paralysis of the tongue and limbs. They are applied as cream-based animal fats to prevent disease and cure gout and sciatica. Traditional medicine makes extensive use of the *A. pyrethrum* herb to treat a variety of ailments. According to a study, stomatitis and stomach disorders are treated with a decoction of *A. pyrethrum* roots (Elhassani et al., 2013).

1.5. Antidiabetic Activity

Since ancient times, herbal remedies have played a significant role in managing diabetes, with many diabetic patients using them as complementary treatments (Saravanan et al., 2020; Ardalani et al., 2021). *Anacyclus pyrethrum* is one such medicinal plant recognized in traditional medicine for its potential to treat diabetes (Bouyahya et al., 2021; Hachi et al., 2016).

A recent review highlighted the findings of an in vivo study by Shahraki et al. (2019), which demonstrated the antidiabetic potential of *A. pyrethrum* root extracts. Diabetic rats treated with an alcoholic root extract (96%) at doses of 100 mg/kg and 150 mg/kg showed significant improvement in tissue damage caused by diabetes. Similar antihyperglycemic effects were observed with an aqueous root extract of *A. pyrethrum* at doses of 250 mg/kg and 300 mg/kg. In these studies, diabetic rats induced with streptozotocin or alloxan displayed a significant reduction in elevated blood glucose levels, which approached normal levels following treatment (Tyagi et al., 2011).

Further investigations on *A. pyrethrum*'s antidiabetic activity revealed its potential to inhibit α-amylase, a key enzyme in carbohydrate metabolism. An in vitro study demonstrated that the ethanolic root extract of *A. pyrethrum* effectively inhibited α-amylase activity in a dose-dependent manner, with an IC_{50} value of 29.25 µg/mL (Selles et al., 2013). This enzyme-inhibitory action supports the potential of *A. pyrethrum* to regulate blood glucose levels by slowing the breakdown of starch into glucose.

The antidiabetic properties of *A. pyrethrum* are believed to be linked to its bioactive compounds, including alkyl amides, alkaloids, and phenolic constituents. These phytochemicals contribute to its ability to regulate blood glucose and improve tissue function. This evidence underscores the therapeutic promise of *A. pyrethrum* as a natural treatment for diabetes. However, further in vivo studies and clinical trials are required to validate its antidiabetic efficacy and ensure its safe use in medical practice (Kumar et al., 2014).

1.6. Anti-Inflammatory Activity

Inflammation is a hallmark of numerous diseases, and *Anacyclus pyrethrum* has demonstrated significant anti-inflammatory effects in various animal models. Studies have shown that extracts of *A. pyrethrum* effectively reduce inflammation-induced edema in rats. Manouze et al. investigated the anti-inflammatory effects of aqueous and methanolic extracts of *A. pyrethrum* roots using two models: Freund's Complete Adjuvant (CFA)-induced paw edema and xylene-induced ear edema in rats. The findings revealed that both extracts significantly reduced paw and ear swelling caused by CFA and xylene, respectively. Oral administration of the extracts at doses of 250 mg/kg and 500 mg/kg alleviated mechanical hypersensitivity induced by CFA. This reduction was observed within 90 minutes of treatment and lasted up to seven hours. Additionally, long-term administration of both extracts showed sustained attenuation of mechanical hypersensitivity in chronic pain conditions caused by CFA (Jawhari et al., 2020).

Further research demonstrated the potent anti-inflammatory activity of aqueous-alcoholic extracts of *A. pyrethrum* leaves, seeds, roots, and flower heads in rat edema models. Oral administration of these extracts led to inflammation inhibition rates ranging from 61% to 71% within one hour of treatment (Jawhari et al., 2021). Interestingly, the inhibition rates were higher (60% to 82%) in groups receiving percutaneous (topical) treatment. For all tested samples, the inhibition percentage continued to rise over a six-hour period, highlighting the sustained anti-inflammatory action of the extracts.

The anti-inflammatory activity of *A. pyrethrum* is attributed to its bioactive constituents, particularly alkaloids like pellitorin and alkylamides. These compounds may inhibit neurogenic inflammation, while flavonoids stabilize cell membranes, reduce vasodilation, and strengthen blood vessel walls, thereby improving vascular integrity. Moreover, another study demonstrated that aqueous, methanol (MeOH), and chloroform extracts of *A. pyrethrum* exhibited notable anti-inflammatory effects, further supporting the plant's potential as a natural anti-inflammatory agent (Crombie et al., 1954).

These findings underscore the therapeutic potential of *A. pyrethrum* as a natural remedy for inflammatory disorders, with its extracts showing significant activity in reducing edema, alleviating hypersensitivity, and enhancing vascular stability. Let me know if you'd like any revisions or further clarification.

1.7. Antioxidant Activity

Extensive research has been conducted on *Anacyclus pyrethrum* to explore its antioxidant potential (Jawhari et al., 2021; Selles et al., 2012; Manouze et al., 2017). One notable study evaluated the antioxidant capacity of methanol (MeOH), aqueous, and chloroform extracts derived from the stems and leaves of *A. pyrethrum* collected in Algeria. This analysis utilized two widely recognized antioxidant assessment methods: DPPH˙ radical scavenging and Ferric Reducing Antioxidant Power (FRAP) assays (Elazzouzi et al., 2019).

Among the tested extracts, the methanol extract displayed the strongest antioxidant activity, with an IC50 value of 0.056 mg/mL, indicating its superior free radical scavenging capacity. The aqueous extract followed, exhibiting an IC_{50} value of 0.114 mg/mL, while the chloroform extract showed relatively lower activity with an IC_{50} of 0.154 mg/mL, as determined by the DPPH˙ assay. Similarly, the FRAP assay revealed that the methanol extract had the highest reducing power, outperforming the aqueous and chloroform extracts (Elazzouzi et al., 2020).

These findings highlight the potential of *A. pyrethrum* as a rich source of natural antioxidants, with the methanol extract demonstrating the most potent antioxidant properties. The significant activity of the methanol extract suggests the presence of bioactive compoundswith strong radical-scavenging and reducing abilities, which could have promising applications in nutraceuticals, cosmetics, and pharmaceuticals.

Table 1. Antioxidant activity of *A. pyrethrum* (var. pyrethrum (L.).

Variety	**Used Part**	**Extract**	**Method**	**Result (in IC_{50} or Absorbance (A))**
var. Pyrethrum	Roots, Flowers, Seeds, Leaves	EtOH	DPPH˙	0.18 mg/mL 0.16 mg/mL 0.01 mg/mL 0.04 mg/mL 0.14 mg/mL

	Flowers, Seeds, Leaves Roots, Flowers, Seeds, Leaves	EtOH	ABTS FRAP	0.07 mg/mL 0.05 mg/mL 0.03 mg/mL 1.19 mg/mL 1.08 mg/mL 0.49 mg/mL 0.38 mg/mL
var. Pyrethrum	Stems, Leaves	MeOH ext. Aqu. ext. Chl. ext.	DPPH·	0.056 mg/mL 0.114 mg/mL 0.154 mg/mL
	Root	MeOH ext. Aqu. ext.	DPPH FRAP BCB DPPH· FRAP BCB	12.38 µg/mL 50.89 µg/mL 107.07 µg/mL 13.41 µg/mL 60.17 µg/mL 120.66 µg/mL
	Root	MeOH ext AcEth ext.	DPPH·	0.15 mg/mL 0.14 µg/mL
		BuOHext HE	DPPH·	0.15 mg/mL 30.50 mg/mL

The antioxidant potential of *Anacyclus pyrethrum* root extracts collected from the Marrakech region of Morocco was evaluated in 2017. Three distinct analytical methods—FRAP (Ferric Reducing Antioxidant Power), BCB (Beta-Carotene Bleaching), and DPPH (2,2-Diphenyl-1-picrylhydrazyl) assays—were utilized for the assessment. The methanol (MeOH) extract exhibited significant antioxidant activity with IC_{50} values of 12.38 µg/mL, 50.89 µg/mL, and 107.07 µg/mL for the FRAP, BCB, and DPPH methods, respectively. The aqueous extract also showed antioxidant effects, with IC_{50} values of 13.41 µg/mL, 60.17 µg/mL, and 120.66 µg/mL for the same methods.

Further investigation of the antioxidant activity of *A. pyrethrum* roots from the Timatidite region of Morocco was carried out by Elazzouzi et al. Their findings revealed that the MeOH extract, butanol (BuOH) fraction, ethyl acetate (AcEth) fraction, and residue (Res) fraction of the root extracts exhibited IC_{50} values of 0.152 mg/mL, 0.155 mg/mL, and 0.144 mg/mL, respectively.

In 2020, the DPPH assay was once again employed to examine the antioxidant properties of *A. pyrethrum* roots. The authors reported an IC_{50} value of 30.50 mg/mL for the root extract, indicating its free radical scavenging potential.

Jawhari et al. recently explored the antioxidant capacity of various parts of two *A. pyrethrum* species—*A. pyrethrum var. pyrethrum* (L.) and *A. pyrethrum var. depressus* (Ball) Maire—obtained from the Timhdite region of Morocco. The study utilized both DPPH and FRAP assays on MeOH extracts from roots, leaves, flowers, and seeds. Among the tested parts, the leaves of *A. pyrethrum var. depressus* (Ball) Maire displayed the highest antioxidant activity with an IC_{50} of 0.03 mg/mL. This remarkable activity was attributed to the presence of phenols, flavonoids, and alkyl amides. In contrast, the seeds of the same variety demonstrated a significant reducing power of 0.25 mg/mL. Additionally, the roots of *A. pyrethrum var. pyrethrum* (L.) exhibited the highest ascorbic acid equivalent antioxidant capacity, measuring 708.74 mg ascorbic acid equivalent per gram of root extract.

Bark is astringent, acrid, cooling, anti-inflammatory, constipating, depurative, and febrifuge. It helps with pitta, burning, inflammations, diarrhea, dysentery, leprosy, skin diseases, pruritus, dyspepsia,

burns, hemorrhages, diabetes, fever, spermatorrhea, and vaginal disorders. Diuretic, carminative, laxative, ophthalmic, and styptic, the leaves help with scabies, burns, tubercular glands, scabies, strangury, dyspepsia, flatulence, scotoma, nyctalopia, ophthalmic, epistaxis, and hemoptysis. Diuretic and aphrodisiac, flowers can help with scabies, urethrorrhea, leucorrhea, splenomegaly, nyctalopia, and anemia.Aphthae, pharyngodynia, and pitta and vat vitiated situations can all benefit from the bitter, acrid, cooling, digestive, carminative, and oleaginous fruits (Chopra et al., 1994). In addition to its traditional use, this herb is used to treat wounds, ulcers, snake bites, and intermittent fever (Kirtikar et al., 1975). A survey of the literature has shown that *D. malabarica* has a variety of phytoconstituents.

CONCLUSION

One of the fascinating medicinal plants in the Asteraceae family, *Anacyclus pyrethrum* and *D. malabarica*, are native to Morocco and Algeria and are used in traditional medicine to cure a variety of illnesses. The literature, botany, traditional usage, phytochemistry, pharmacological use, and toxicity of *A. pyrethrum* have all been covered in this review. The information gathered supports this species' pharmaceutical potential. Actually, various pharmacological properties, including anti-inflammatory, antidiabetic, and antioxidant properties, have been investigated in experimental research. Numerous studies have also demonstrated the species' abundance in secondary metabolites, including as alkaloids, polyphenols, and terpenoids. These support its widespread usage in traditional medicine. It is important to note, nonetheless, that research on the separation and fractionation of its components is few.

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