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Review

A review on dicarboxylic acids and their derivatives used to treat diabetes

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Abstract

Diabetes mellitus is a chronic and complex condition that disrupts how the body breaks down proteins, fats, and sugars. It is described as being incapable of decreasing the blood sugar levels. Type 1 diabetes is caused by β cell failure in the pancreas, whereas type 2 diabetes is caused by insufficient insulin and the body's resistance to it. Diabetes is considered a common disease. There are many drugs and techniques put into practice to control diabetes. The current drugs for diabetes, including insulin and other agents, have some problems. These include needing to be used for a long time, having bad side effects, and being expensive. Due to these problems, people are more likely to look for safer and cheaper medicines, such as plant-based medicines. The plants, which have natural ingredients, are now being studied in research.

Keywords: Diabetes mellitus, Phytochemicals, Anti-diabetic drugs

INTRODUCTION

Diabetes is a multiple, intricate metabolic condition characterized by elevated levels of glucose in the blood caused by either insufficient insulin production, resistance to the effects of insulin, or both. Gestational diabetes, type 1, and type 2 are the most common types. [1]

Type 1 diabetes mellitus

The main feature of Type 1 Diabetes Mellitus is the destruction of beta cells producing insulin in the islets of Langerhans of the pancreas, which exists in 5% to 10% of those affected by diabetes. This leads to no insulin available. Autoimmunity is connected to a complex interaction of environmental factors including toxins, specific viruses, and other foods along with certain genetic predispositions. Type 1Diabetes Mellitus can happen at any age, but it is most often seen in children and teenagers. [2]

Type 2 diabetes mellitus

About 90% of diabetes patients have type 2 diabetes. Type 2 diabetes is a condition where there is a condition known as insulin resistance. Insulin resistance means that the body does not respond well to insulin. Here, insulin cannot perform its task well, and the body begins producing more insulin to maintain normal blood sugar levels. However, over time, this increases, resulting in type 2 diabetes. Most people with type 2 diabetes are over 45 years of age. However, the incidence of obesity, physical inactivity, and high-calorie diets is increasing among children, adolescents, and young adults. [3]

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM), commonly well known as hyperglycemia in pregnancy, is the term used to describe hyperglycemia that is initially identified during pregnancy. Gestational diabetes often affects pregnant women in the second and third trimesters, while it can happen at any time. The American Diabetes Association (ADA) estimates that 7% of pregnancies are complicated with Gestational Diabetes Mellitus. Type 2 diabetes mellitus is more likely to develop in the future in women with gestational diabetes mellitus and their children

Hypertension, preeclampsia, and hydramnios can aggravate Gestational Diabetes Mellitus, and it may also result in more surgical procedure. The fetus may have congenital defects macrosomia, or excessive weight and size. These babies may have respiratory distress syndrome even after delivery, and they may go on to develop childhood and teenage obesity. Obesity, advanced age, substantial weight gain after pregnancy. [4]

Insulin insufficiency and resistance (type 2) or complete loss of function of the β cells of the islets of Langerhans (type 1) are the causes. Diabetes is seen as a widespread illness. Diabetes is treated using a variety of methods and drugs. Long-term use, negative side effects, and high cost are some of the drawbacks of the present antidiabetic medications, such as insulin and agents. Due to these restrictions, there is a greater propensity to look for drugs that are less harmful and more reasonably priced. Plant-based medicines are the best solution for the treatment of a variety of diseases their phytochemicals play a key role in treating a variety of health complications. Phytochemicals like alkaloids, flavonoids, terpenoids, tannins, and phenols, Dicarboxylic acids consist of different pharmacological properties in treating many diseases like diabetes, cancers, various type of cardiovascular diseases, asthma, arthritis, neurological disorders, inflammations, etc, Phytochemicals have been proven to have antioxidant and anti-inflammatory properties which are meant or treating different types of diseases. [5]

Some of the Phytoconstituents which are proven for antidiabetic activity.

❖ **Alkaloids**

Aegelin, Marmesin and Marmelosin

Aegelin, marmesin, and marmelosin are major alkaloids from the plant *Aegle marmelos* that promote pancreatic β cell regeneration and insulin secretion. These botanicals aim to repair pancreatic β cells and maintain insulin levels by increasing insulin gene expression, secretion, and inhibition. Patients with Type 1 Diabetes Mellitus (T1DM) have no functional β cells, leading to depletion and reliance on exogenous insulin. Other botanicals include Tribulus terrestris extracts, β carbolines, Achyranthes aspera extracts, Xanthocercis, Zambesiaca, Berberine, and Castanospermum australe, which have been shown to inhibit DPP-IV and control hyperglycemia in experimental rats. [6]

Catharanthine, vindoline & vindolinine

Alkaloids including catharanthine, vindoline, and vindolinine derived from the source *Catharanthus roseus*, which is a member of the Apocynaceae family, were shown to reduce the glucose levels in blood in both healthy and streptozotocin-induced diabetic rat animals. Vindoline, catharanthine, leeurosine, and vindoline reduce glucose levels in blood in the both healthy and alloxan-induced diabetic rabbits. In some regions of the world, particularly India, the West Indies, and Nigeria, dimeric alkaloids called vincristine and vinblastine, which are extracted from the leaves and branches of Catharanthus roseus, have been used to treat diabetic mellitus. [7]

❖ **Phenols**

Chlorogenic acid

According to reports, Chlorogenic Acids derived from a variety of plant sources have positive anti-diabetic benefits. Numerous scholars have examined the potential mechanism underlying its anti-diabetic effects. Using Lepr db/db mice, recently investigated the mechanisms via which Chlorogenic Acid has anti-diabetic benefits. According to the research, Chlorogenic acid activated the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway, which in turn promoted glucose absorption by the skeletal muscle cells. [8]

Ellagic acid

Ellagic acid is a polyphenolic substance mostly present in nuts and fruits. The administration of Ellagic acid has been shown to have strong anti-diabetic benefits in several in-vitro and in vivo investigations. In type 2

diabetic-insulin resistant albino rats showed that a two-week combined therapy with repaglinide of dose (0.5 mg/kg) and Ellagic Acid of dose (10 mg/kg) enhanced lipid profiles, glucose balance and insulin signaling. [9] In another research, Ellagic acid administration at a dosage of 50 mg/kg/day for 28 days decreased blood glucose levels in female rats. Then, it activated the liver's insulin signaling pathways, as seen by elevated phosphorylated. [10] It was also shown that ellagic acid increases insulin release from isolated mouse islet cells stimulated with glucose. A dosage of 25 mg/kg did not significantly alter glucose tolerance in type 2 diabetic rats given with ellagic acid, according to the oral glucose tolerance test.[11] However, 50 mg/kg and 100 mg/kg doses enhanced glucose tolerance.

❖ **Flavonoids**

Rutin

Rutin's anti-diabetic properties include lowering the absorption of carbohydrates from the small intestine, improving tissue uptake of glucose, suppressing tissue gluconeogenesis, activating insulin secretion from β-cells, and shielding the islets of Langerhans from the degenerative changes. Additionally, rutin reduces the production of pro-inflammatory cytokines, sorbitol, reactive oxygen species, and precursors of advanced glycation end products. [12]

Morin

Morin is a naturally occurring flavonoid that is mostly found in fruits like guava and figs, as well as traditional medicinal plants like *Prunus dulcis* and *Chlorophora tinctoria* L. [13] In animal models, oral morin treatment for 30 days significantly improved insulin resistance, hyperglycemia, and glucose tolerance. Following morin administration, lipid peroxides and antioxidant levels were shown to have decreased in diabetic rats. [14] Morin's anti-inflammatory benefits are demonstrated by the efficient reduction of inflammatory cytokines such as TNF-α and IL-6. Morin restored leptin sensitivity in animal models, and hepatic insulin decreased hyperlipidemia and liver lipid buildup. Morin has varying effects on hepatic enzymes, notably decreasing the activity of Fructose-1,6-diphosphatase (FDPase) and G6Pase while increasing the activity of hexokinase and G6PD.

❖ **Coumarins**

Osthole

In vitro experiments and a diabetic db/db mouse model demonstrate the hypoglycemic effect. Osthole was found to directly inhibit peroxisome proliferator-activated receptors (PPAR), steroid transcription factors that affect the expression of multiple target genes involved in glucose metabolism and fatty acid storage, for the treatment of hyperlipidemia, hyperglycemia, and insulin resistance. [15] Osthole was administered in various ways to obese diabetic db/db mice, and it was discovered to lower blood glucose levels. Osthole may thus be a dual PPAR inhibitor, considerably reducing hyperglycemia, as demonstrated by the findings of the in vitro and mouse model studies, making it a promising novel medication for the treatment of diabetes mellitus. [16]

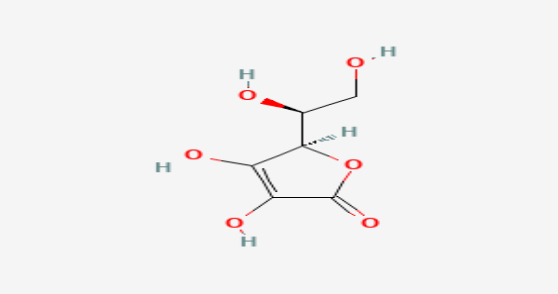
Dicarboxylic acids

Dicarboxylic acids are natural compounds that are found in plants they are widely used in food industries, pharmaceutical industries, and animal research to know the potential pharmacological action of different classes of Dicarboxylic acids, according to the previous literature on the Dicarboxylic acids like sebacic acid, ascorbic acid, malic acid, succinic acid, glutaric acid was used in different animal model screening methods for knowing the pharmacological effect of the Dicarboxylic acids. They have been proven for anticancer, chemopreventive lipids [17] antimicrobial, antidiabetic, antimetabolite, anti-inflammatory [18] antihelminthic, and antioxidant, anti-viral, Neuroprotective agents in treating various neurological disorders and neuroinflammatory diseases. [19]

Review of literature Dicarboxylic acids and their pharmacological effect- literature review findings

Ascorbic acid

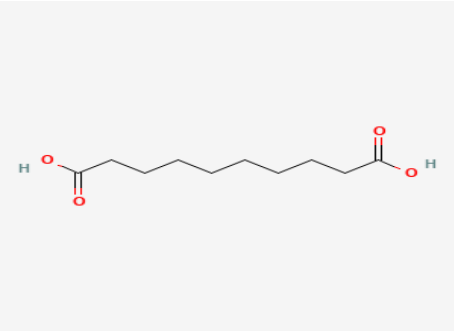
Ascorbic acid, also referred to as vitamin C, is a potent water-soluble antioxidant that protects against oxidative stress-induced tissue damage and scavenges excess free radicals in diabetic patients' bodies. According to some research, ascorbic acid supplementation can help people with type 2 diabetes by enhancing islet cell activity. [20] This can be utilized to address issues later on and prevent diabetes in the first place, Moreover, ascorbic acid supplementation has been demonstrated in certain studies but not in others to improve insulin resistance and control fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c). [21] The basic exogenous vitamin ascorbate is well-known for its potent anti-inflammatory and antioxidant qualities. Ascorbate prevents oxidation of proteins, lipids, and DNA, which stops inflammation and cell death. Its ability to stop DNA mutation, inflammation, and cell death, particularly in cancer cells. [22] Also been proven to prevent various cardiovascular diseases, in the treatment of gastrointestinal diseases, and in the treatment of neurodegenerative diseases. Ascorbic acid has played a fantastic role during COVID-19 due to its prooxidant nature it has played a crucial role during the pandemic. [23]



Ascorbic acid

Sebacic acid

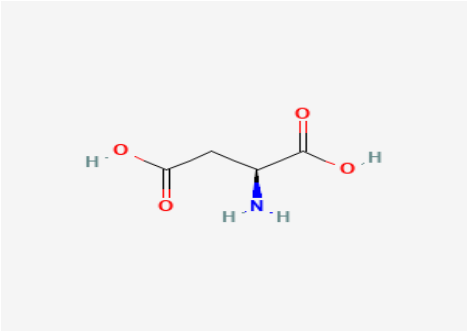
Research on type 2 diabetes in humans and animals revealed that oral sebacic acid with the combinational treatment of other Dicarboxylic acids- Dodecanedioic acid, decreased hepatic gluconeogenesis and glucose production while improving glycemic control, most likely via increasing insulin sensitivity. [24] Additionally, dodecanedioic acid consumption decreased exercise-induced muscular tiredness in individuals with type 2 diabetes, indicating improved energy use and metabolic flexibility. [25] From previous literature studies, sebacic acid has been proven for pharmacological effects like antimalarial, antispasmodic, anti-inflammatory, antileishmanial, effect, anti-oxidant effect. sebacic acid with a combination of anti-inflammatory and antimalarial. [26]



Sebacic acid

Aspartic acid

According to the previous literature, Asparates have proven that they played a role in hepatic fibrosis regulation in an animal liver fibrosis model. The mice were exposed to 2% CCl_4 for four weeks, leading to significant collagen deposition and widespread fibrosis. After four weeks, the mice were given Asparates or a stock meal, and the histopathological changes were observed. Asp-co-treatment completely abrogated the fibrogenic response in the liver but there is no proper evidence about aspartic acid treating diabetes. [27] Previous studies have shown that it has a pro-anti-inflammatory effect in treating inflammation of the liver. Further investigations must be done to evaluate the anti-diabetic activity.

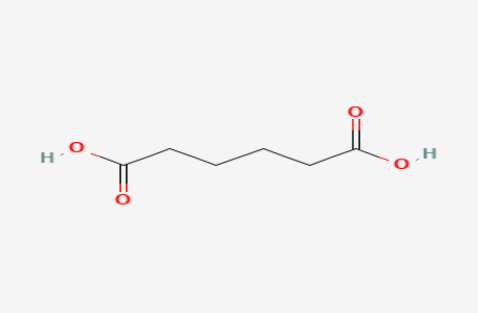


Aspartic acid

Adipic acid

Adipic acid is a class of dicarboxylic acid also known as Hexanedioic acid. According to the previous literature, adipic acid is an active component, instrumental in treating or avoiding insulin resistance syndrome, fatty liver (ideally non-alcoholic fatty liver), diabetes, obesity, and dyslipidemia. In addition to having therapeutic

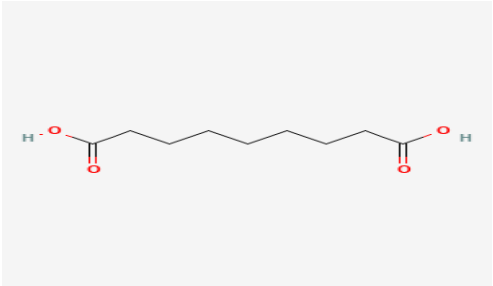
efficacies for obesity, dyslipidemia, or fatty liver, the composition of the current invention can be used as pharmaceuticals or functional foods. [28] It also significantly lowers blood insulin and fasting glucose levels, which can help treat type 2 diabetes, insulin resistance, and other metabolic disorders. Aspartic acid has been enrolled as an "acidity regulator" in additives in the food database of the Domestic Food Code, It is also registered as an acidity regulator in the Food and Color Additive Database of the U.S. FDA. [29] Additionally, it has been also reported as an anti-ketogenic agent and anti-hypertensive agent in rats. [30]



Adipic acid

Azelaic acid

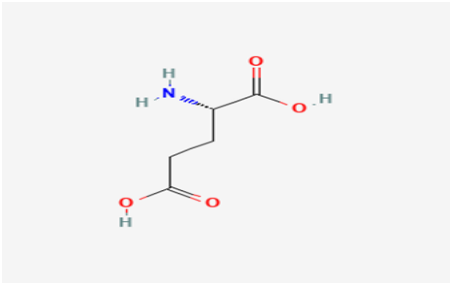
Azelaic acid is a naturally occurring saturated Dicarboxylic acid that is non-phenolic and generated by the yeast Malassezia. Its physiological actions are varied and include antibacterial, anti-keratinizing, anti-melanogenic, anti-inflammatory, and antioxidant properties. Pharmaceutically, Azelaic acid is FDA-approved for treating papulopustular rosacea and is used extensively in dermatology. [31,32] It is also very effective in treating melasma and acne vulgaris. Through an In-vivo anti-inflammatory test, the azelaic acid (mixed with 30% ethanol) was applied to the swollen ear of the test group of rats, and inflammation in the rats' ears was cured within 24 hours compared to the untreated groups, hence proving for its anti-inflammatory activity. [33]



Azelaic acid

Glutamic acid

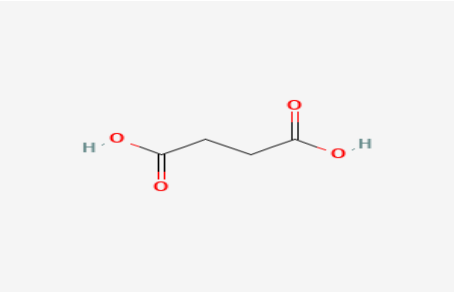
Glutamic acid is one of the dicarboxylic acids which were used in treating different types of diseases and disorders, glutamic acid is generally prescribed with hypertensive medicine, it is used for the treatment of pulmonary atrial hypertension a condition where high blood pressure in the lungs makes it difficult for the heart to pump blood efficiently. It is also used as an anticancer agent in treating cancers, immunomodulator, used to improve the potency of the neurotransmitters in humans, glutamines play a main role in maintaining and increasing the release of the growth hormone in children, they undergo metabolism to act as fuel for the various organs in the body but, there is no proper evidence that glutamic acid in treating or preventing diabetes but it has the efficacy of maintaining the normal blood glucose level in human and maintaining the acid levels in the intestines. [34]



Glutamic acid

Succinic acid

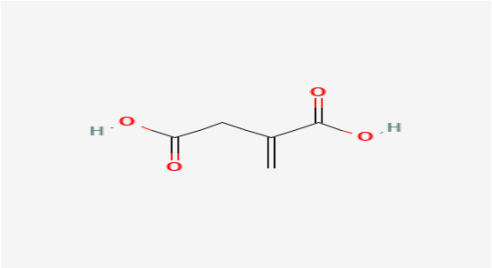
Succinic acid is one of the widely used substances in treating metabolic disorders. The previous study investigated the effect of Succinic acid mono-ethyl ester (EMS) and the Effects of metformin on tissue lipid profile, lipoproteins, lipid peroxidation, insulin, plasma glucose, and serum in streptozotocin-nicotinamide-induced type 2 diabetic rats. Results showed that succinic acid mono-ethyl ester and metformin reduced glucose in plasma while boosting insulin levels and reducing lipids in serum, tissues, and lipid peroxidation products. The study suggests succinic acid mono-ethyl ester may have antihyperlipidemic properties. Besides its antidiabetic action, it also has antiperoxidative benefits. [35]



Succinic acid

Itaconic acid

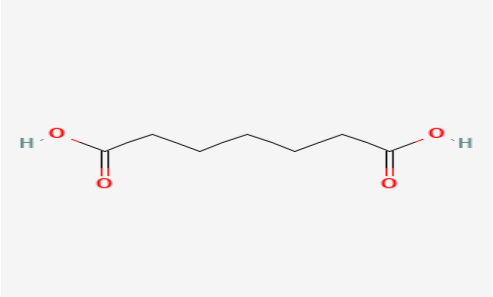
Itaconic acid is one of the dicarboxylic acids that were primarily used as an immunomodulator in treating autoimmune disorders, itaconic acids were not used directly in treating diseases its derivatives were used to treat diabetic wounds by using mice in the *invivo* studies by observing the fibrinogen(nanofiber)structure production in diabetic wounded animals by its anti-oxidant and anti-inflammatory effect. [36] By blocking isocitrate lyase, the primary enzyme of a crucial route (glyoxylate shunt) for bacterial growth in vivo, itaconic acid has been demonstrated to have antibacterial properties. [37] By regulating the generation of reactive oxygen species (ROS), itaconic acid can help prevent bacterial and viral infections. This mechanism is thought to be shared by several antibiotics. [38]



Itaconic acid

Pimelic acid

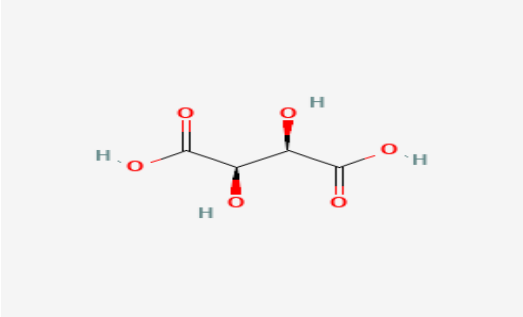
Pimelic acids are a class of dicarboxylic acids. These compounds are used in pharmaceuticals and cosmetics, but there is no proper evidence for their pharmacological effect in previous studies. As per previous literature, the overall medium-chain-dicarboxylic acids have been mentioned that they have potent antioxidant, anticancer, anti-inflammatory, glucose regulation, antibacterial, etc. [39]



Pimelic acid

Tartaric acid

Tartaric acid is one of the dicarboxylic acids. Tartaric acid derivative in Streptozotocin-diabetic rats, L-Tartaric Acid was able to enhance oral glucose tolerance (OGT), raise the amount of glycogen in the liver and extensor digitorum longus (EDL) muscle, and dramatically lower glycemia. It also improved the lipid profile and atherogenic indices. So Tartaric acid has been proven for anti-hyperglycemic and anti-lipidemic effects. [40]



Tartaric acid

CONCLUSION

This review shows how significant dicarboxylic acids are as a topic for several scientific studies. Current studies in pharmacology have confirmed the health benefits associated with dicarboxylic acids. To establish the basis for the nine compounds (Sebacic Acid, Succinic Acid, Azelaic Acid, Glutamic Acid, Adipic Acid, Itaconic Acid, Tartaric Acid, Aspartic Acid, and Pimelic Acid) and their possible use in research, it also gathers data from many studies. However, some of the compounds' potential for treating or preventing diabetes lacks adequate evidence, and more research is necessary to determine their pharmacological effects.

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