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Identification and Antidiabetic Activity of Coumarin in Aegle Marmelos

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ABSTRACT

Diabetes mellitus, one of the primary metabolic illnesses, affects 2.8% of people worldwide and is predicted to rise to 5.4% by 2025. The use of herbal treatments in modern, high-tech medicine is expanding, as they have long been considered as a highly effective source of medication. In light of the aforementioned factors, the current review presents profiles of the plant Aegle marmelos, which has hypoglycemic properties. These profiles are based on literature sources from numerous databases, and they are properly categorized according to the parts used, the method of lowering blood sugar (insulin mimetic or activity of insulin secretagogues), and the active phytoconstituents that have insulin mimetic activity. According to the review, plants with hypoglycemic potential primarily belong to the Rutaceae family. As a result, the analysis largely concludes that the presence of coumarins and other elements that demonstrate a decrease in blood glucose levels is what gives Aegle marmelos its antidiabetic properties. The research also covers how these plants' active ingredients can be used to manage diabetes mellitus.

Keywords: Diabetes, Coumarin, Aegle Marmelos, Insulin Secretagogues, Insulin Mimetic, Phytoconstituents, Blood Glucose, Antidiabetic Activity, Medicinal Plant, Herbal Medicine, Diabetes Mellitus, Hypoglycemic Activity.

I. INTRODUCTION

The importance of plant-based medicines for the treatment of many ailments has significantly expanded during the past few years. Native Indian cultures in India pay a great deal of attention to natural items because of their numerous medical qualities. This medical approach is less hazardous, pollution-free, and side effect-free. Only 350 species, mostly herbs, out of the 6000 plants specified in ancient medical systems are used.[2]

An example of such a plant is the aegle marmelos, which is referenced in the ancient Sanskrit medicinal classic Charak Samhita. It is a well-known medicinal plant that has been employed in traditional medicine for many years, as well as in the Ayurvedic and Siddha schools of medicine, to cure a variety of diseases. Rutaceae is the family that includes Aegle Marmelos, also called Bael.[3]

Plant profile:

- Biochemical Name: Aegle Marmelos
- Indian Name: Bilva
- Name in English: Bael Tree
- Family: Rutaceae
- Used plant parts include fruit, leaves, roots, and bark.

classification in science:

- Kingdom: Plantae
- Order: Sapindales
- Family: Rutaceae
- Subfamily: Aurantioideae
- Tribe: Clauseneae
- Genus: A. Correa
- Species: A. marmelos

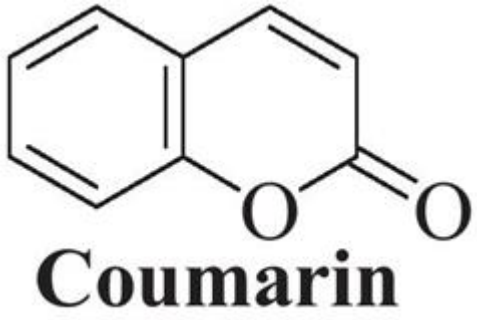
Numerous investigations have been carried out to ascertain the specific composition of the leaves, fruit pulp, and seed powder of Aegle Marmelos. A good source of protein, fat, minerals, crude fibre, and energy is bael leaf, pulp, and seed powder. They are also a great source of nutritional fibre and quickly digestible carbs. It was found in a study that used normal methods to assess the values for the approximate composition of Aegle Marmelos leaf, pulp, and seed powder that it contains antinutrients that help regulate blood sugar.

Aegle marmelos is a plant that is commonly used in Indian Ayurvedic medicine to cure diabetes. In rats with streptozotocin-induced diabetes, mellit soral and intraperitoneal administration of the plant's aqueous extract from various sections had a hypoglycemic effect. Because the extract can significantly lower blood glucose and glycosylated haemoglobin levels while also raising plasma insulin and liver glycogen in diabetic rats, the extract exhibits a multimodal anti-diabetic mode of action. The well-known hypoglycemic drug glibenclamide was outperformed by a 250mg/kg dose of the leaf extract in terms of efficacy. By promoting the release of insulin from the islets of Langerhans' pre-existing beta cells, Coumarin and Marmesin found in the Bael leaf extract imply that the leaves have antioxidant capability and may contribute to the antidiabetic action. Numerous bioactive substances found in the leaves are recognized to provide health advantages and serve as nutraceuticals. Additionally, because of its usual flavor and nutrient composition, it can be utilized as a food ingredient. The discovered compounds may be crucial in the creation of drugs, food preservation, and health supplements due to their strong antibacterial and antioxidant capabilities as well as additional therapeutic possibilities. [4]

Coumarin:

Tonka beans (Dipteryx odoranta wild Fabaceae family) were the first plant from which coumarins were extracted in 1820. The family of benzopyrones includes coumarin. They are chemicals that are either naturally produced from plants or synthetically created, inhibiting a wide range of biological functions and providing a more extensive therapeutic profile.

A sweet, vanilla-like scent and a bitter taste characterise coumarin. It is a solid, crystalline, colourless material. It is found in many plants and may serve as a chemical defence against predators by suppressing the production of vitamin K. A related molecule is used to create the prescription medication warfarin, which acts as an anticoagulant to prevent blood clots, deep vein thrombosis, and pulmonary embolism.



Coumarin

The benzene and -pyrone rings that make up the phenolic substance known as coumarin are fused together. Coumarins come in at least 1300 different varieties. The coumarins' antithrombotic and vasodilator characteristics. In order to treat vaginal candidiasis, some coumarin compounds exhibit antibacterial properties, such as an inhibitory impact against C. albicans. Gram-positive bacteria can be inhibited by hydroxycinnamic acids, and phytoalexins are thought to have antifungal properties.

At various phases of cancer development, coumarins shown anticancer properties through a variety of methods, including cell cycle arrest, cell death, oestrogen receptor modulation, or inhibition of DNA-associated enzymes such topoisomerase.[5]

MOA of Coumarin on Diabetes:

Blood glucose levels rise because of an imbalance in glucose homeostasis brought on by the chronic metabolic disorder diabetes mellitus. The research of powerful tiny molecules anti-diabetic activity is one of the most exciting disciplines due to the tremendous rise in diabetes prevalence in recent decades. Coumarins participate in the healing process or amelioration of symptoms associated with diabetes by acting on a variety of targets associated with the disease in various ways. A complicated biology underlies diabetes.

The small intestinal mucosa's brush border has a high concentration of -glycosidase, which has a significant impact on the structure of glycosyl groups. They have the ability to break down polysaccharides like sucrose, maltose, and starch into monosaccharides. It increases blood glucose by cleaving the glycosidic linkages in different sugar molecules either by endo or exo cleavage. The three primary types of sugary compounds that remain after hydrolysis are monosaccharides, oligosaccharides, and carbohydrate complexes. Acarbose and voglibose, two commonly used traditional -glucosidase inhibitors, have gastrointestinal adverse effects such nausea and vomiting. 3-(4'-Benzoyl amino-phenyl) was studied by Hu and colleagues. The inhibitory effects of coumarin derivatives on -glucosidase varied from those of positive control drugs, but they were all lower than 65 mol/L, according to screening results. Compound 27 displayed stronger inhibitory properties.[1]

Aim

Metabolic disorder called diabetes with a wide range of aetiologies that is characterised by abnormalities in protein, carbohydrate, and lipid metabolism due to deficiencies in the secretion and/or action of insulin. According to a study by the International Diabetes Federation (IDF), smoking and high blood pressure are the two other main risk factors for premature mortality. An anti-diabetic chemical known as coumarin was discovered in the leaves of the Aegle marmelos plant to counteract the side effects of anti-diabetic drugs. Reduce mortality, maintain excellent quality of life, avoid or delay the onset of late disease sequelae, and prevent or delay the beginning of acute decompensation are the research's overarching goals.

Objectives:

- Coumarin is widely used and found wide range of applications particularly in cosmetics and pharmaceutical industries.
- The coumarin shows properties like antibacterial, antimicrobial, antiviral, anti-inflammatory, antioxidant and enzyme inhibitory activities but we found that as like above effect coumarin also shows antidiabetic activity.
- The glycoside collected from the plant extract of Aegle marmelos which shows presence of coumarin that shows antidiabetic activity.
- In this research we found the new method of checking UV absorbance of coumarin extract.
- The extract we collected shows various activities.
- The main objective research is to overcome the side effect of antidiabetic drugs.
- Easy collection of plant extract because plant is easily available.

Need for study:

Numerous types of foreign publications in recent years have demonstrated the efficacy of coumarin and its derivatives in treating diabetic complications like nephropathy and cardiovascular disease. In this study, we examined coumarin's anti-diabetic properties, which aid diabetic patients in managing their condition and reducing their chance of developing complications. The effects of coumarins against diabetes and its consequences in vivo and in vitro are the main topic of this study. Traditional medicine has a promising future in the treatment of diabetes mellitus and has a strong track record in clinical practise. Globally, 422 million individuals have diabetes, up from 108 million in 1980. Diabetes is a leading cause of lower limb amputation, renal failure, heart attack, and blindness. With diet, exercise, medication, regular screening for problems, and treatment of those issues, diabetes can be treated, and its effects can be postponed or prevented. Herbal medications have gained tremendous popularity in recent years, both in developed and developing countries, due to their natural sources and lack of side effects.[1]

II. METHODS AND MATERIAL

Collection of material:

The leaves of Agele marmelos are collected from the surrounding of AMIPSR save, and authenticated by Yashwantrao Chavan Warana Mahavidyalay Warananagar. The authentication certificate no. AMIPSRS/ 1074/ 2022-23. Soon after collection the leaves are cleaned and kept for drying. The leaves are powdered using mortar and pastel. The powder was stored in an air tight container, until further use.

Preparation of extraction:

The extraction was prepared using the maceration method. As part of the maceration extraction process, menstruum is poured on top of coarsely powdered drug material, such as leaves, stems, bark, or root bark. This process continues until the drug material is completely soaked. After that, the container is sealed and maintained for at least seven days. The mixture needs to be shaken if it's in a container and occasionally combined to accomplish complete extraction. Filtering is used to separate the micelle from the marc after extraction.[6]

Maceration process

For the process ethanol was taken as solvent with distilled water. The ratio for powder and solvent was 1:16. And for solvent 70:30 ratio was taken. For the required extraction 85 gm. powder of Agele marmelos leaves was taken. The powder was placed inside conical flask. 952 ml of ethanol is mixed with 408 ml of distilled water and poured in conical flask. The conical flask is fully sealed using the cotton and aluminum foil. The extract is kept for 7 days with continue stirring.

Filtration of Extract:

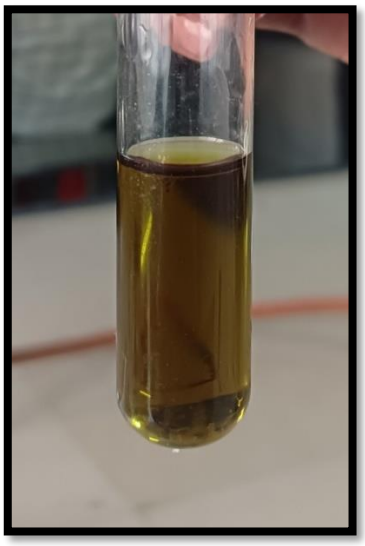
The extraction of solution is done by simple filtration method using filter paper. The liquid extract was collected in volumetric flask and stored for further process.

Filtration of extract

Identification test for glycosides:

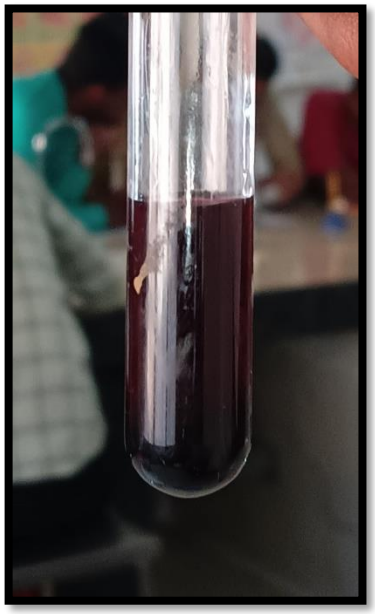
In living organisms, glycosides perform a variety of essential roles. In many plants, inactive glycosides serve as the main chemical storage form. Enzyme hydrolysis, which removes the chemical from the sugar component and renders it useful, can be used to activate these. These plant glycosides are frequently used in medicine. As part of their removal from the body, toxins in both humans and animals are frequently attached to sugar molecules, known as aglycones. Any naturally occurring substance, including terpenes, flavonoids, Coumarin, and many more, can be this substance. There are numerous ways to join the glycone to the aglycon. However, it can also be carbon (C-glycoside), nitrogen (N-glycoside), Sulphur (S-glycoside), or oxygen (O-glycoside). Oxygen is the most typical bridging atom. Typically, one based on the arrangement of the hemiacetal hydroxyl group, distinguishes between -Glycosides and Glycosides. The majority of glycosides that are found in nature are -glycosides. Because glycosides are often more polar than aglycones, the o-coumaric acid lactone known as Coumarin is primarily found in glycosides from plants. The majority of coumarins come from plants, where they are found as glycosides. Consequently, it is crucial to identify glycosides in order to identify Coumarin.[7]

1. LEGAL test: 2 ml of extract was added with 2 ml of pyridine and few drops of 2% sodium nitropruside with 20% NaOH. Brownish colour observed. So the glycosides are present in the given extract.[8]

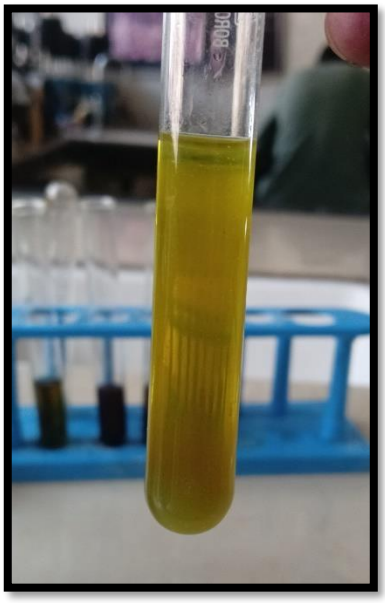


LEGAL TEST

2. LIEBERMAN`S BURCHARDS TEST: 2ml of extract, 2ml of acetic acid, 2ml of carefully applied conc. H2SO4, and 2ml of cooling water. Greenish brownish light colour is visible. There is a steroidal nucleus. Consequently, the glycosides exist. [8]



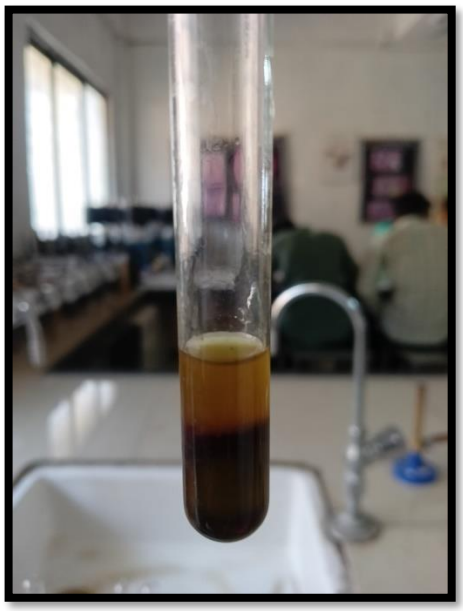
LIEBERMAN`S BURCHARDS TEST



KEDDE TEST

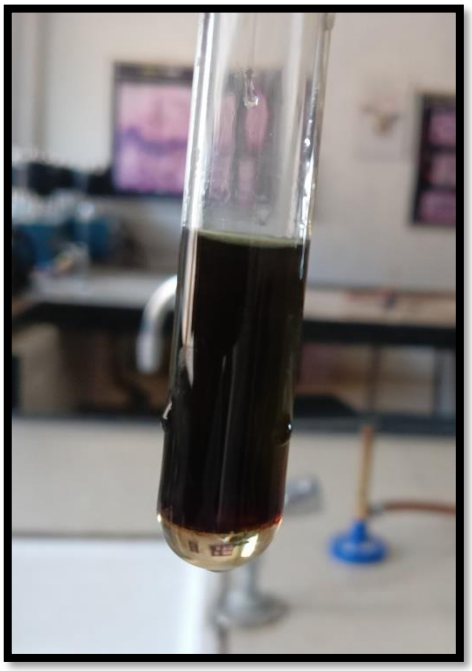
3. SALKOWASKI TEST: To dissolve the extract, 2ml of it was carefully added to 2ml of chloroform. At the interface, a steroid ring with a dark reddish brown hue may be noticed. Glycosides are present. [8]

5. KELLER-KILIANI TEST: FeCl3 and H2So4 are combined with 2ml of extract and 2ml of glacial acetic acid. brownish greenish ring. Cardenolides have a de-oxy sugar flavour. [8]



SALKOWASKI TEST

4. KEDDE TEST: 2ml of extract adding with 3.5 dinitrobenzoic acid in methanol with NaOH. No ring is observed. So the glycosides are absent. [8]



KELLER-KILIANI TEST

Confirmation test for Coumarin:

Coumarin is the *o*-coumaric acid lactone found mostly in the glycoside form in plants. Plants are the major

source of coumarins. These occur as glycosides. Four out of five identification tests for glycosides were present. Coumarin is a glycoside so the confirmation test for Coumarin was performed as follow:

1. Fluorescence test
2. Ferric Chloride test
3. Paper chromatography test

1. Fluorescence test:

Few drops of alcoholic extract were taken in test tube. 1 ml of NaOH solution was added in extract the blue green fluorescence was generated which indicates the presence of Coumarin.[9]

Fluorescence test

2. Ferric chloride test:

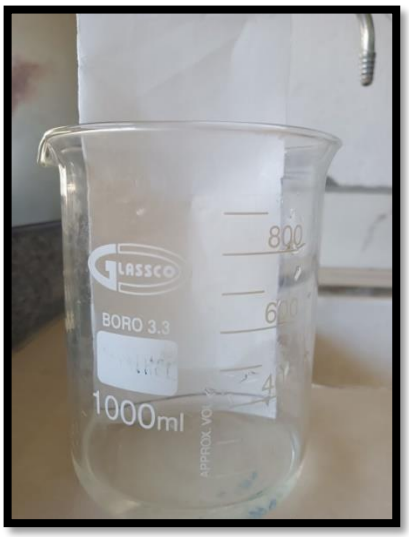
Alcoholic extract of drug sample was taken in test tube and few drops of alcoholic $FeCl_3$ solution was added the dark green colour was appeared. After the addition of conc. HNO_3 it turns yellow which directly indicates the presence of Coumarin.[10]

Ferric chloride test

3. Paper chromatography test:

It appeared plausible that the coumarins might also be separated and possibly identified in this way given that the roughly related flavones and their glycosides have been successfully separated and identified using the paper chromatography approach. Gauge et al. (1951) and Dent, Stepka & Steward (1947) both used solvent systemsAccording to their reports, the luminous compound created by Bowman & Hanning (1951) from potato tubers migrated. Additionally, they released the RF values for aesculetin in several solvent systems. In a range of solvent solutions, the RF values of numerous natural coumarins and closely related cinnamic acid derivatives have been computed. Additionally, the visible and fluorescent colours that various chromogenic sprays produce when applied to the produced chromatogram have been established. It is advised to think that the findings will provide a way to find coumarins in extracts from natural sources. Out of the more than fifty solvent systems that were examined, only those that offered trustworthy and useful results are presented here. Effective separations have been demonstrated using single-phase solvent solutions that only contain water. Since the order of the two phases is quite different, it has been demonstrated that the aqueous layer of two-phase systems can occasionally provide separations that are just as excellent as those produced by the organic layer.

These divisions might be useful for several kinds of molecules. Tests using ortho dihydroxy grouping materials on sodium borate-treated filter paper and carboxylic acid grouping materials on sodium phosphate-treated paper yielded findings that support this theory.[11]



The fundamental idea might be partition chromatography or adsorption chromatography. Water that is entrapped in the pores of the filter paper and a mobile phase that permeates the paper make up the two phases. The mobile phase's mobility causes the mixture to separate. The chemicals in the mixture separate under the capillary action of paper pores in accordance with variations in their affinities towards stationary and mobile phase solvents. In an adsorption chromatography procedure, where liquid acts as the mobile phase, paper's solid surface serves as the stationary phase. The sheets were all obtained from the same batch of Whatman No. 1 filter paper and ran through the same direction. Ethyl acetate was used to create the mobile phase. Additionally, an alcoholic extract of Agele marmelous was taken as a stationary phase. The coumarin's optimal Rf value is 0.95.[11]

R_f value calculation:

$$R_f = \frac{\text{Distance traveled by solute}}{\text{Distance traveled by solvent}}$$

R_f = 12.6/13.5

= 0.93

The ideal value as per the reference is 0.95 and as per calculation the resultant value is 0.93. This shows the presence of coumarin in the given extract.[11]

From the all the identification test it shows the presence of coumarin in the given extract.

Identification of antidiabetic leads from coumarin through absorbance test on UV:

Preparing the solutions:

1. Coumarin standard stock solution:

Place 100 ml of ethanol in a volumetric flask, and precisely weigh 1.0 ml of coumarin extract into it.[12]

2. Coumarin standard solution (100 mg/ml):

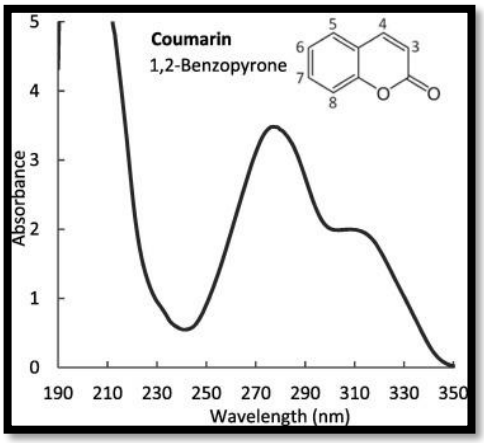
Put ethanol into a 500 ml volumetric flask after precisely weighing 5 ml of the coumarin standard stock solution in it.[12]

3. Coumarin standard solution (1 mg/ml):

Place 500 ml of ethanol into a volumetric flask after precisely weighing 5 ml of coumarin standard solution in it.[12]

The recorded absorbance of coumarin according to reference is 274. [12]

The ideal absorbance curve for coumarin:



The absorbance curve of coumarin performed in AMIPSR, save:

According to the readings taken on UV the resultant absorbance is 275. The data used to support the presence of coumarin in the given plant extract.

III. CONCLUSION

For a number of reasons, there are still lots of people who turn to the conventional medical system. Due to factors including growing populations, a lack of medical supplies, side effects from various allopathic medications, and diseases that are becoming more resistant to current treatments, there is an increasing emphasis on using plant material as a source of human medicines. The use of this plant in various types of medicine is firmly believed to be supported by comprehensive data, such as the data given in this study on the petrochemicals and diverse biological properties of plant extract. Historically, Aegle marmelous (Bael) has been used for a number of ethano botanical uses. Today, aegle marmelos are a major source of medicine used to treat a number of human and animal illnesses. Jam prepared from the leaves of the Aegle marmelous plant should be widely advertised as a health tonic in addition to researching techniques to make standardised pharmaceuticals from diverse Aegle marmelous plant parts. Sadly, most of the substances have not been carefully examined in order to identify new lead molecules or pharmacophore. The mechanisms of a few bioactive compounds' activities have also so far been identified.

For the first time, coumarin, a promising antidiabetic agent, was successfully isolated from Aegle marmelos in the current investigation. Future research might be thought of as beginning with these findings. To turn it into a novel diabetic medicine, toxicology studies may be proposed in the future.

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