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An Advanced Phytotherapy Approach For Hepatoprotective Activities Using Capsules Delivery Systems Incorporated With Aloe Barbadensis Extract

Gaurav Pratap Singh[1], Arti Akash Bhimanwar[2], Jaya Vasavi Gurrala[3*], Nayana Shivaji Baste[4], Sachin Tyagi[5], Lokesh Agrawal[6], Dharmendra Singh[7], Kiran Singh[8]

[1]Assistant Professor, Dr.K.N. Modi Institute of Pharmaceutical Education And Reasearch, Kapra Mill, Opposite SBI Branch, Modinagar, Ghaziabad, Uttar Pradesh. 201204

[2]Associate Professor, Jayawantrao Sawant College of Pharmacy And Research, Hadapsar, Pune, Maharashtra. 411028

[3*]Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Sree Balaji Medical Colleges And Hospitals, BIHER, Chrompet, Chennai, Tamilnadu. 600044

[4]Associate Professor, SNJB's Shriman Sureshdada Jain College of Pharmacy, Chandwad, Nashik, Maharashtra, India. 423101

[5]Professor & Director, Bharat Institute of Technology, School of Pharmacy, Meerut, Uttar Pradesh. 250103

[6]Universidad integral Del Caribe y America Latina, Kaminda Cas Grandi # 79 Willemstad, Curacao Neural Circuit Unit, Okinawa Institute of Science & Technology Graduate University, 1919-1 Tancha, Onna, Kunigami District, Okinawa, Japan. 904-0412

[7]Assistant Professor, Institute of Pharmacy, Veer Bahadur Singh Purvanchal University, Jaunpur, Uttar Pradesh, India. 222003

[8]Assistant Professor, Institute of Pharmaceutical Sciences, University of Lucknow, Uttar Pradesh, India.

Corresponding Author: Jaya Vasavi Gurrala

[3]Associate Professor, Department of Pharmaceutics, Faculty of Pharmacy, Sree Balaji Medical Colleges And Hospitals, BIHER, Chrompet, Chennai, Tamilnadu. 600044

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Abstract

Numerous medicinal plants have shown promise in treating a wide range of illnesses due to the presence of active components. Phenols, coumarins, lignans, essential oil, monoterpenes, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthenes are among the chemical components found in liver-protective plants. Since many plants and formulations are purported to have hepatoprotective properties, there has been a significant focus on developing hepatoprotective medications derived from plants on a global scale. Traditional medicine makes extensive use of Aloe barbadensis for a variety of conditions, one of which is its hepatoprotective action. Capsules of Aloe barbadensis were prepared and tested for organoleptic qualities and other metrics. Results from the finest in-vitro dissolution tests showed that the Aloe barbadensis extract medicinal herbs capsules could be a promising new phytotherapy strategy for hepatoprotective effects, with a rate of 89% after 10 minutes in acid medium. The current study demonstrates that the aqueous extract of Aloe barbadensis has a substantial ability to restore the integrity of hepatocytes, as demonstrated by improvements in physiological parameters, excretory capacity (BSP retention) of hepatocytes, and stimulation of bile flow secretion.

Keywords: hepatoprotective, Organoleptic properties, Medicinal herbs, Aloe barbadensis ect.

Introduction

Developed and developing nations alike rely on plant-based medicines, both as home cures and as ingredients for pharmaceuticals. This sector accounts for a sizable chunk of the worldwide drug market. Our body metabolites create toxins, which are the primary cause of liver injury. The primary goal of herbal treatments is to provide a non-invasive means of alleviating liver problems [1]. Many people are turning to medicinal herbs and phytonutrients, often known as nutraceuticals, for treatment of a wide range of health issues in healthcare systems around the world. These herbal medicines are now widely available in grocery stores and health food stores, attesting to the enormous upsurge in popularity of natural therapies over the last decade in both developed and developing nations [2]. Traditional medicine, which includes the use of herbs, is considered an essential aspect of the culture in those communities. It is believed that four billion people, or 80% of the global population, reside in the developing world and depend on herbal medicinal products as their main source of healthcare. For primary health care, between 75 to 80% of the global population still relies on herbal medicine, primarily in underdeveloped nations. Due to their low cost, high effectiveness, and relative safety, herbal medications from Indian traditional medicine have been increasingly popular in recent years [3]. When it comes to treating liver disorders, the Indian traditional medical system has long relied on a number of medicinal herbs. Medicinal plants and their derivatives have a long history of usage as natural treatments for liver problems, and this practice is continued in many forms around the globe today. The active components in plants are frequently the ones responsible for their medicinal effects, according to scientific studies. Numerous medicinal plants have shown promise in treating a wide range of illnesses due to the presence of active components. Phenols, coumarins, lignans, essential oil, monoterpenes, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthenes are among the chemical components found in liver-protective plants [4]. Since many plants and formulations are purported to have hepatoprotective properties, there has been a significant focus on developing hepatoprotective medications derived from plants on a global scale. Many different types of liver problems can now be prevented and treated with phytomedicines, which are medicinal plants or herbal remedies. The hepatogenic or hepatoprotective effects of these plants have only been demonstrated in a small number of the plants and formulations studied experimentally [5]. Herbal medications for serious liver disorders need to be thoroughly tested for characteristics like antiviral activity (hepatitis B, hepatitis C, etc.) in order to get appropriate results. Cholestatic action, anti-hepatotoxicity (antioxidants and others), and liver-regenerative stimulation. It is quite probable that the needed activities to cure severe liver illnesses will be provided by a combination of various herbal extracts or fractions. Medicinal herbs have anti-hepatotoxic effects due to the presence of phytochemicals, which are powerful antioxidants[6]. Research into herbal medicine has been spurred by the increasing number of people suffering from liver dysfunction as a result of excessive alcohol and drug use. Reason being, treating common liver disorders including cirrhosis, fatty liver, and chronic hepatitis is challenging because there aren't many solutions that work for everyone. Herbal remedies have a long history of usage in Eastern medicine for the treatment of liver and internal organ diseases, and they are now gaining popularity as a treatment for pathological liver illnesses on a global scale [7]. Though hundreds have been explored, few have been investigated in depth. People believe that herbal medications are safe to use since they are 'natural,' and their perception of their efficacy in treating and preventing disease is reflected in their increasing use.[8]. This article summarizes prior research on the following topics: the efficacy of herbal extracts in liver disease treatment, the mechanisms by which herbal medicines work, the history of our knowledge of herbs' hepatoprotective properties, and the difficulties scientists encounter when trying to identify and study each herb's individual compounds.

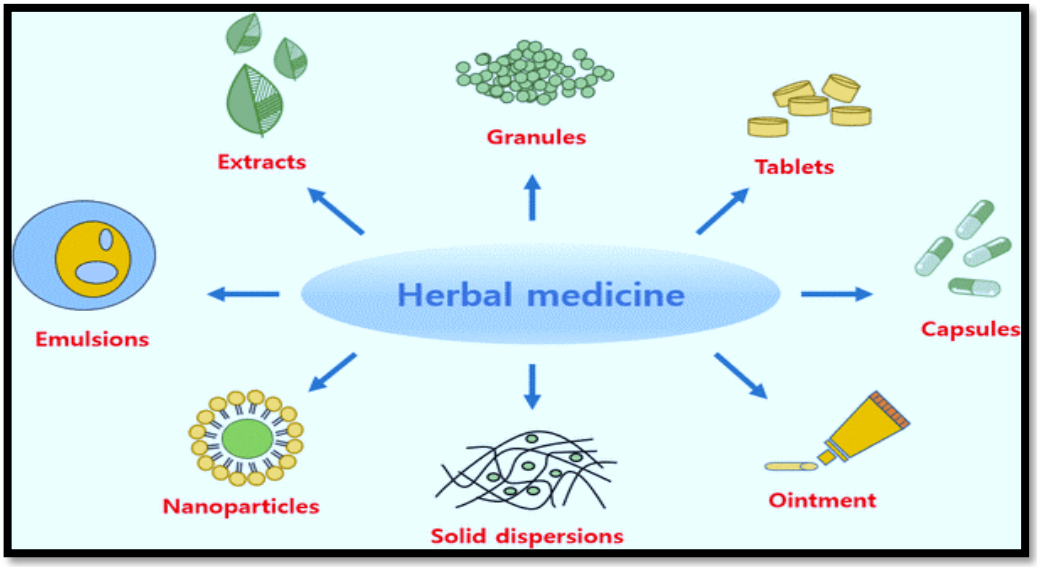

Fig.1 Flow diagram of Herbal medicine and their various formulations

Chemical constituents present in Aloe barbadensis Extracts[9]

Chromone and anthraquinone, as well as its glycoside derivatives, are the two primary classes of active constituents found in the extract of the Aloe vera plant [10].

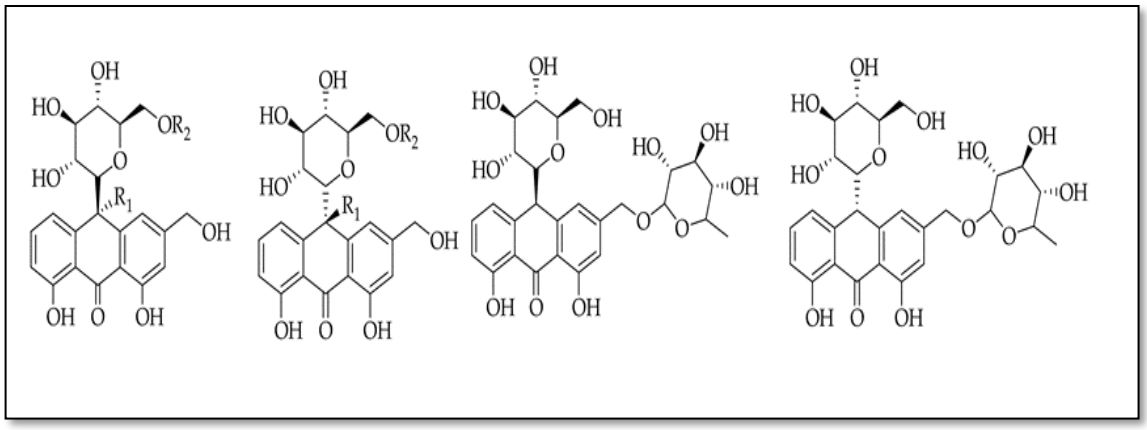

Fig.2 Aloe barbadensis glycoside anthraquinone and its molecular structure

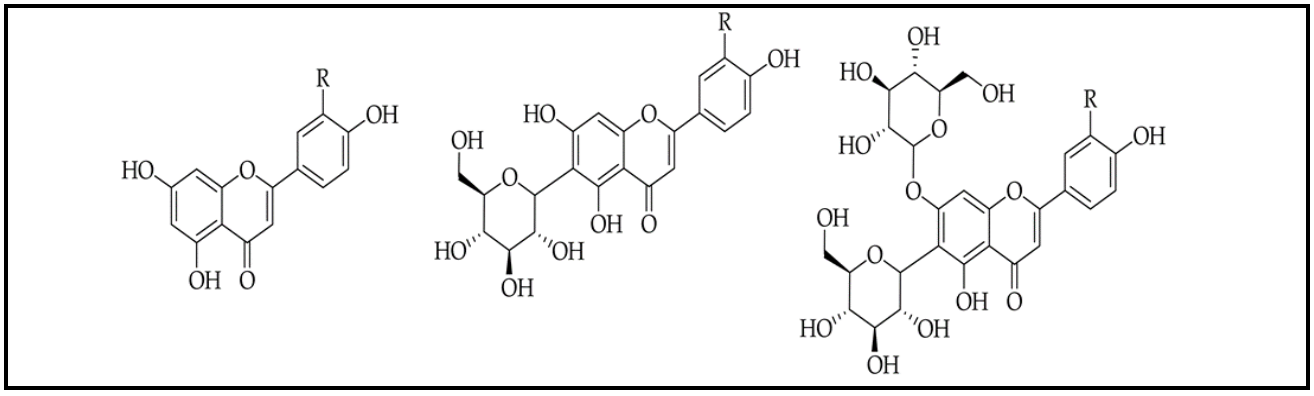

Fig.3 Molecular chemical formula of the flavonoids found in Aloe barbadensis

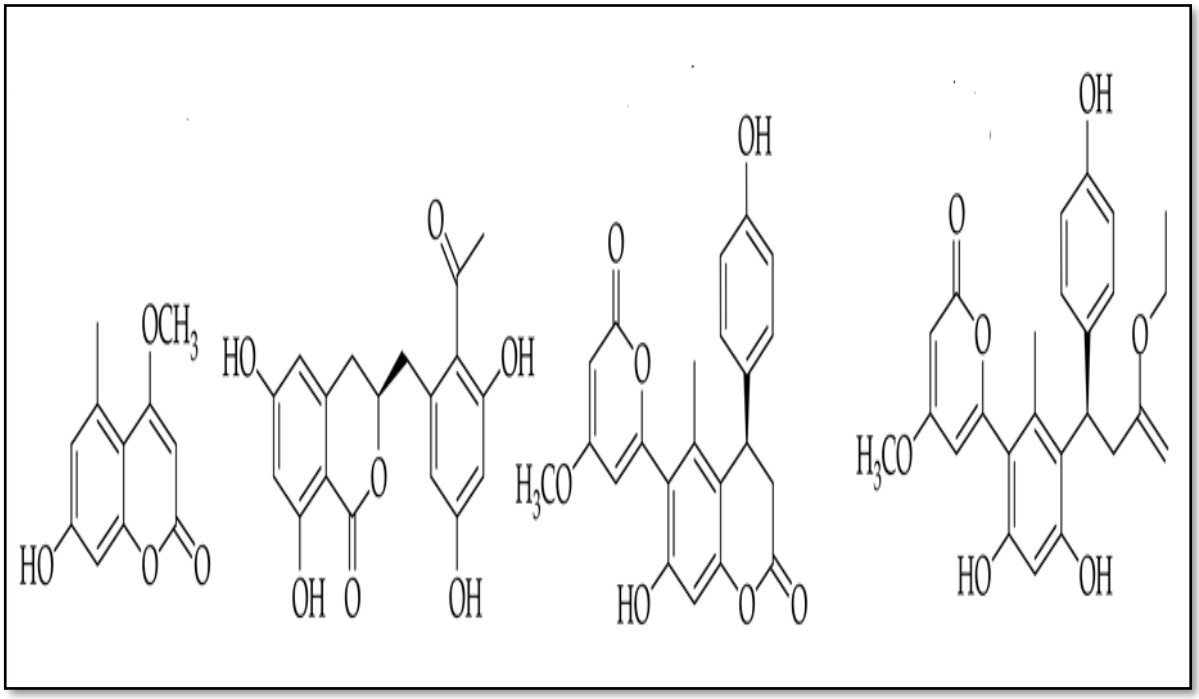

Fig.4 Phenylpropanoids isolated from Aloe barbadensis and their chemical structure

Formulation of Capsules [12]

Many pharmaceutical and nutraceutical medications come in capsule form, which is ideal for oral administration. Capsules typically contain one dose of the active substance and come in a variety of shapes, sizes, and materials. A number of excipients, such as antimicrobial preservatives, fillers, flavoring agents, sweeteners, and coloring agents, are included in the fill material with the active medicinal ingredient or primary nutrition 12].Branding and dosage information can be printed on the exterior of medication capsules. Depending on the pharmacological component or, in the case of nutraceuticals, the form of the major nutrient, the capsules might contain solid, liquid, or paste substances. The outer capsule shell is unaffected by any solvents or excipients that may be present in the active pharmaceutical ingredient (API).

Advantages and Disadvantages of Capsules[13]

Using Capsules for Maximum Benefit: Ideal for impromptu compounding, these hard-gelatin capsules allow for dosing and ingredient combinations to be tailored to each individual patient. It is more stable than liquid medication types. smaller than standard tablet and pill sizes, allowing for quicker solubility and absorption in bodily fluids. Can mask the odor and taste of medicine in liquid form; suitable for use in depot capsules and enteric coated capsules; concentration dependent.

Capsule Drawbacks: Incompatible with highly soluble substances; when ruptured, the concentrated solution will come into touch with the stomach wall, causing irritation and tension. Not suitable for use with highly efflorescent or deliquescent materials. It took a long time to compound, the bitter drug causes vomiting and corrosiveness, which are difficult to overcome, and the efflorescent material makes the capsule soft while the deliquescent ingredient makes it brittle and easily broken.

Capsule Types: Among the many types of capsules are: Separated into hard capsules and soft capsules according to consistency. In light of the following usage guidelines: Administration routes: orally, intrarectally, and vaginally. Applying the Considering the intended use: Hard gelatin for humans Finished product: The capsule's hard gelatin exterior is composed of: Fundamental components: Sugar, water, gelatin, and other substances: Colourants, antioxidants (such as SO2), lighteners (such as TiO2), and taste enhancers [14].

The active components in hard gelatin capsules are solid. The process of making the capsules involves putting pin shapes resembling fingers into a liquid gelatin solution, removing them, and letting the resulting layer of gelatin dry. After the film dries, the pins are removed and the capsules are cut. All you need is the right medication or nutraceutical ingredient, and the capsules come with their caps and bodies already unlocked. Pharmaceutical capsules might contain more than one kind of medication. It is usual practice to have the medications in various forms in this situation; for instance, one may be in the shape of a tablet and another a smaller capsule. The bigger pill can thereafter contain both medications.

The gelatin in soft gelatin capsules, often known as soft gels, is occasionally plasticized with sorbitol or glycerin to make them thicker than hard gelatin capsules. The specifics of the encased substance as well as external factors like air temperature and humidity are considered by the producer when deciding on the gelatin thickness. Soft capsules' gelatine recipe could call for additives such colors, dyes, and preservatives. You can also add sweeteners and flavorings[15].

The active chemicals are released when the encapsulating material reaches the intestinal fluid, where it breaks down at a higher pH, after resisting the acidity of the stomach. Because capsules composed of gelatin are vulnerable to microbial attack and growth, it is critical to keep an eye out for microbial contamination during production, packing, storage, and delivery of capsules. This work developed and tested a novel phytotherapy strategy for hepatoprotection using Aloe barbadensis freeze-dried extract powder in a solid dose form as a medicinal herb capsule delivery system.

Materials and Methods

Ingredients such as hard gelatin capsules (size 00), colloidal silicon dioxide (Aerosil), magnesium stearate, microcrystalline cellulose (MCC), hydrochloric acid (0.1NHCl), a buffer solution with a pH of 6.8, citric acid, and ethanol were procured from Sigma Aldrich. The freeze-dried ethanol extract of Aloe barbadensis was formulated and acquired from the Dept. of Biological Sciences at Rani Durgavati Vishwavidyalaya in Jabalpur, M.P. The analytical grade chemicals and other materials were generously provided by the merck Pharmaceutical Industry Company in India.

Formulation and Evaluation of Aloe barbadensis Extract[16,17]

Assessment of the Extract's Olfactory Characteristics [18]

We tested the extract for the following organoleptic traits: Outward manifestations, aroma, and flavor. Using the five senses—sight, smell, touch, and taste—the Aloe barbadensis powder was examined and evaluated.

Fig. 2: Plant and Powder of *Aloe barbadensis* Flowers Extract.

Measurement of the Solubility of Aloe barbadensis Extract[19,20]

The solubility of a chemical is primarily determined by the choice of solvent, as well as the prevailing temperature and pressure conditions. The solubility of a substance in a particular solvent is determined by its saturation concentration, which is the point at which adding more solute does not result in a rise in its concentration in the solution. Consequently, a significant number of generic medication manufacturers are more likely to produce oral drug formulations that are bioequivalent. The solubility application is determined based on the conventional characteristics of solubility, as indicated in Table 1.

Table 1: Solubility parameters at standard level [21]

Description	Part of solute in part of solvent
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

Some preformulation metrics, including bulk density, tap density, and Carr's index, were determined by analysing the powders. Precisely pour a specified amount of powder into the measuring cylinder, ensuring that the powder remains level without being compressed. If needed, adjust the powder to get the desired level. Then, read the volume of the powder, labeled as Vo,

without any disturbance, rounding to the nearest graded unit as indicated in Table 2.
Calculate the bulk density, in gm per ml, by the formula.
Bulk density = Bulk Mass/ Bulk Volume
Carr's compressibility index:

Carr's index (%) = (Tapped density – Poured density) / Tapped density

Table 2. Carr's Index Parameters of Powder Flowability.

% Carr's index	Nature of Flow
5 -15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
>40	Extremely Poor

Measurement of the Extract's Flowability[22,23]

The angle of repose (θ) is a significant metric that characterizes the flowability of a powder. For the test, a unique equipment was utilized in this investigation. On one side of the plate was a glass cylinder, and on the other was a plate with a scale and a ruler to determine how high the powder mound should be. Ten grammes of plant extract that had been filtered through a 180-degree sieve was placed into a glass cylinder to determine the angle of repose. The next step was to carefully raise the cylinder, which let the powder spill out the bottom and settle into a conical mound on the plate. This process and its results are documented in Table 3.

Table 3: The Flow Properties of Powder and Angle of Repose.

Flow Property	Angle of Repose (Degrees)
Excellent	<20
Good	20-30
Passable	30-34
Very poor	>40

Development of Aloe barbadensis Extract Capsules[24,25]

The process involves combining the semisolid extract of Aloe barbadensis with microcrystalline cellulose, mg stearate as a lubricant, and colloidal silicon dioxide (Aerosil) as a glidant. The resulting mixture is then put into capsules according to the specifications stated in Table 4.

Table 4: The Formulation of *Aloe barbadensis* Extract Capsules

S.No.	Chemicals & Ingredients	Required Amount (mg)
01	*Aloe Rubroviolaceae*	250mg
02	Microcrystalline Cellulose	230mg
03	Mg Stearate	10mg
04	Colloidal Silicon Dioxide (Aerosil)	10mg

Measurement of Weight Uniformity and Quantity of Aloe barbadensis Capsules[26]

The British Pharmacopoeia technique was employed to ascertain the homogeneity of weight. To determine the average weight (mass) of the substance, twenty capsules of Aloe barbadensis were

prepared and their contents were weighed individually. There could be no more than a 7.5% discrepancy between the average and any two of the individual weights; in fact, no discrepancies were larger than that. The amount of powder that was actually put into the capsules was checked against the amount that was desired, and the discrepancy between the two was calculated. The formulation specified that one capsule should be filled with 250mg of Aloe barbadensis extract. A total of twenty capsules were selected at random. The contents of each capsule were weighed, and the percentage difference between the actual weight and the required weight was computed. These differences were then averaged across all twenty capsules to determine the accuracy of the filling process.

Capsules of Aloe Barbadensis Extract Weighed for Moisture Content [27]

Because it can induce their destruction, water has a significant impact on the physical and chemical stability of pharmaceutical preparations and active medicinal components. Bacteria thrive in the presence of water, which is present in many pharmacological compounds and preparations. In the gastrointestinal tract, bacteria may die and endotoxin may be released if an organism absorbs a composition that contains a specific quantity of bacteria. Several factors affect the amount of water present in a solid, including the substance's composition, its degree of fragmentation, the solution it is created in, and the surrounding temperature and humidity.

In-Vitro Dissolving Rate of Capsules Containing Aloe Barbadensis Extract[28]

As a measure of the bioavailability and quality of a pharmaceutical product, the dissolving test determines how quickly a medication is discharged into solution from a dosage form. So that testing processes can be made easier. The researchers in this study utilized the paddle method. We found the maximum UV absorbance of Aloe barbadensis extract solutions at 330 nm, which allowed us to quantify the amount of extract dissolved.

Table 5: The Organoleptic Properties of Aloe barbadensis Extract [29]

Properties of Extracts	Aloe barbadensis Extract
Physical Appearance	Free-Flowing, Small Particulate Powder
Color	Darken Brown
Odor	Unpleasant Odor
Taste	Bitter

Patient acceptability of dose forms is often low due to their disagreeable smells and bitter taste. Hopefully, when the extract is put into capsule form, these undesirable qualities will be less noticeable.by means of a UV-VIS Spectrophotometer. Here are the requirements and procedures that were followed for the dissolution study:

Apparatus: Paddle.

Medium: pH 6.8 citric acid buffer. Volume of medium:900ml.

Condition: 37±0.5°C. Revolutions per minute: 100 rpm. Estimated dissolving times are 10, 20, 30, 40, 50, and 60 minutes. The apparatus's vessel was filled with 900 ml of degassed citric acid buffer with a pH of 6.8, and then heated to 37±0.5°C in a water bath. Each vessel had one capsule added to it before the paddle was lowered into position and the equipment was turned on at a speed of 100 rpm. Three milliliters (ml) of the medium was removed at 10, 20, 30, 40, 50, and 60 minutes after the commencement from a point halfway between the surface of the dissolving medium and the top of the revolving paddle, and no less than 10 mm from the vessel wall. On

each occasion, 3 ml of a citric acid buffer with a pH of 6.8 was added to the tank to replace the removed medium. The solution's ultraviolet absorbance was measured at the previously indicated wavelengths, with a blank reference solution.

Results and Discussion

Effects of Freeze-Dried Aloe Barbadensis Extract on Odor and Taste

The freeze-dried extract's organoleptic qualities are displayed in Fig. 3, as well as in Table 5. A drug's bioavailability is greatly affected by its water solubility when administered orally in solid dosage forms. Table 6 shows the results of the solubility testing of the Aloe barbadensis extract, which indicate that the extract is soluble in water.

Table 6: Evaluation Parameters of *Aloe barbadensis* Extract.

Testing	*Aloe barbadensis*
The Solubility of Extract	Water Soluble
Tapped Density	2.70
Carr's Index (%)	11%
Angle of Repose (°)	23.30°
The Moisture Content (%)	2.0%

The Powdered Extract Densities After Freezing

According to Table 5, all of the freeze-dried extract powders of Aloe barbadensis exhibit good flow qualities, with a compressibility index of 11% and a tapped density of 2.96.

The Powdered Freeze-Dried Extract's Flowability

Results showed that there was a 9.92% average weight variance for Aloe barbadensis capsules. Table 7 shows that the Aloe barbadensis capsules were found to be within the specified limit set by the British Pharmacopoeia, which is the maximum allowable departure in weight from the average for capsules.

The Uniformity of Weight and The Amount of *Aloe barbadensis* Extract Capsules

Table 7: The Uniformity of Weight and Content of Aloe barbadensis Extract Capsules.

S.No.	Capsule Empty Weight in(g)	Capsule Weight After Filling (g)	Deviation in Weight - Average %
1	0. 102	0.497	10.6
2	0.105	0.504	12.5
3	0.101	0.496	10.6
4	0.101	0.501	11.9
5	0.104	0.495	9.30
6	0.105	0.498	9.90
7	0.102	0.495	9.78
8	0.103	0 .504	10.8
9	0.103	0.497	10.5
10	0.105	0.501	10.2
Average	0.1031	0.4988	9.92

Aloe Barbadensis Extract Capsules In-Vitro Dissolve Test

In a 10-minute period, 85% of the Aloe barbadensis capsule contents dissolved in acid media, according to the results of the dissolving studies (Table 8). The findings in the acid medium are in accordance with the standards defined by the British Pharmacopoeia. They suggest that the Aloe barbadensis capsules are solid oral dosage forms with rapid release, high bioavailability, and invitro disintegration. The dissolution of 24.73% of the Aloe barbadensis capsule contents in a buffer media with a pH of 6.8 was observed within 60 minutes, as shown in Table 9. Aloe barbadensis powder had angles of repose of 22.30^0 and the results showed that the buffer pH of 6.8 did not meet the standards specified by the British Pharmacopoeia. Consequently, it exhibited wonderful flow characteristics. As can be seen in Table 5, this meant that the freeze-dried powders of Aloe barbadensis had the right amount of water-holding capacity to be made into capsules.

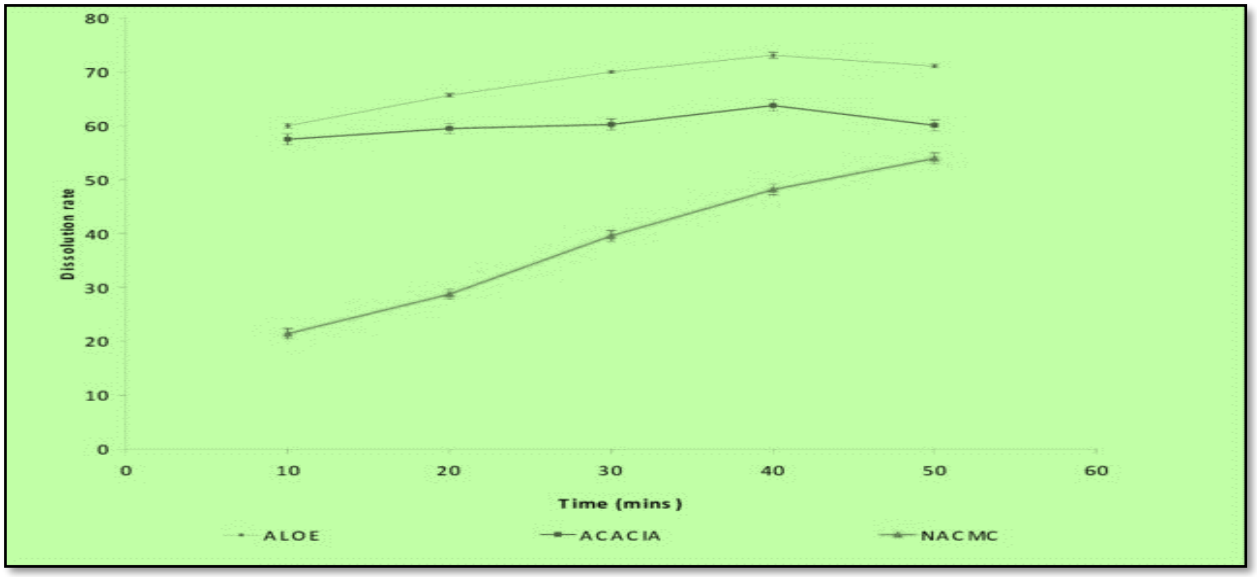

Fig.3 Graph represent the In-Vitro dissolution rate of Aloe Barbadensis Extract Capsules

Aloe barbadensis extract capsules' moisture level

In the preformulation investigation, the results showed that the Aloe barbadensis extract had a moisture content of 1.7%, whereas the Aloe barbadensis capsule contents had a moisture level of 7%. The result was that the Aloe barbadensis material seemed to have a somewhat higher moisture content following encapsulation. Because of its hygroscopic properties, this extract may have absorbed some moisture throughout the filling process.

Table 8: The Drug Release Percentage of Aloe barbadensis Extract Capsule in Acid Medium.

Time (min)	Amount Dissolution%
10	85
20	93
30	94.35
40	95.53
50	96.21
60	96.69

Table 9: The Drug Release Percentage of Aloe barbadensis Extract Capsule in Buffer pH 6.8.

Time(min)	Amount Dissolution%
10	14.69
20	15.02
30	17.43
40	18.05
50	22.24
60	24.63

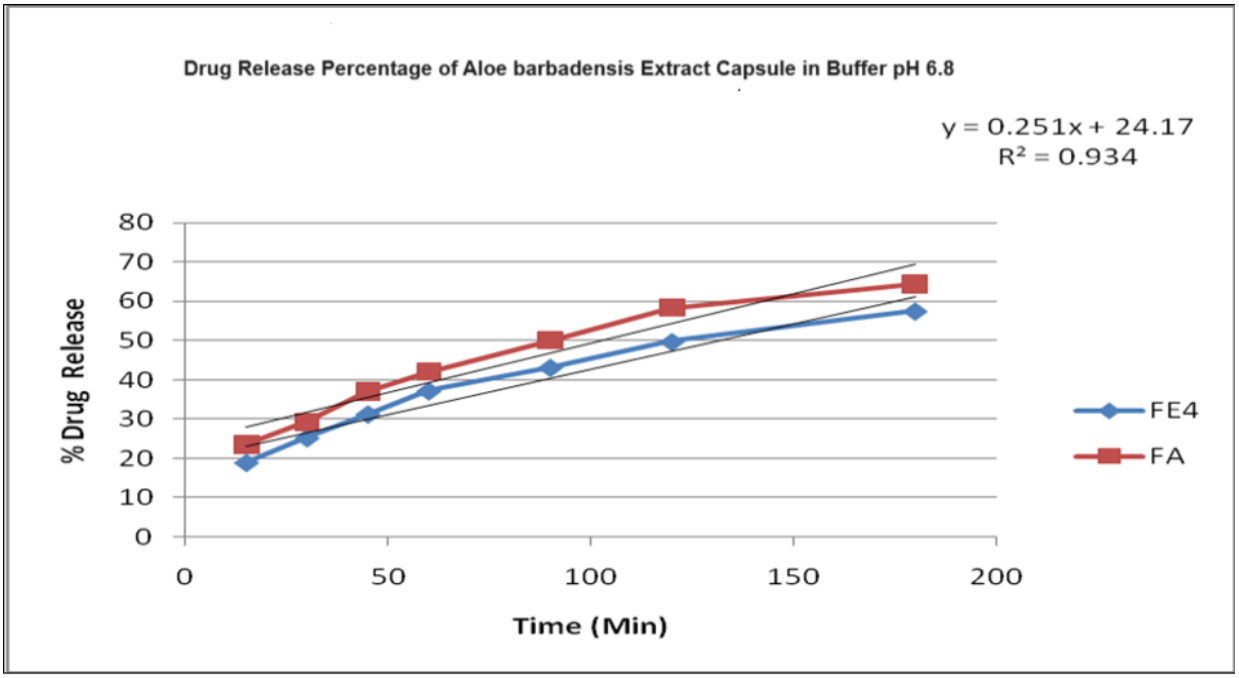

Fig.4 Drug Release Percentage of Aloe barbadensis Extract Capsule in Buffer pH 6.8

Hepatoprotective activity

The concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamine transferase (GGT), alkaline phosphatase (ALP), and total bilirubin (TB) in the serum were measured using commercially available kits from Spinreact, Spain, following the instructions provided by the manufacturer. The concentration of total protein (TP) was determined using the Biuret method as described in a commercially available kit (HELFA, Diagnostics, Cuba). The levels of serum total cholesterol, triglycerides (TG), and high-density lipoproteins cholesterol (HDL-c) were measured.

The measurement of low-density lipoproteins cholesterol (LDL-c) and very low-density lipoproteins (VLDL-c) was conducted.

Statistical Analysis.

Statgraphics plus (version 5.0.1 for Windows, MA, USA) was used to carry out the statistical analysis. The one-way analysis of variance (ANOVA) and Tukey HSD test were carried out to compare the groups that were statistically different. Values of $p < 0.05$were considered significant.

Table No. 10 Corporal weight gain and relation between rat liver and final corporal weight (standard deviation on parenthesis).

Group Weight	Initial body(g)	Final body weight	Body weight gain	Liver weight	Liver weight/final
I	176.3(12.23)	212.2(13.42)	35.84 (3.25)	3.49 (0.80)	1.64 (0.22)
II	189.2(13.88)	194.70 (17.40)	5.46 (1.99)	4.85 (0.86)	2.49 (0.51)
III	175.2(12.26)	214.8(25.21)	39.58 (4.52)	3.41 (0.75)	1.59 (0.29)
IV	181.36(12.54)	223.4(13.15)	42.11 (4.12)	3.86(0.65)	1.72 (0.35)
V	191.8(13.47)	229.9(16.6)	38.07(3.57)	3.75(0.92)	1.63 (0.26)

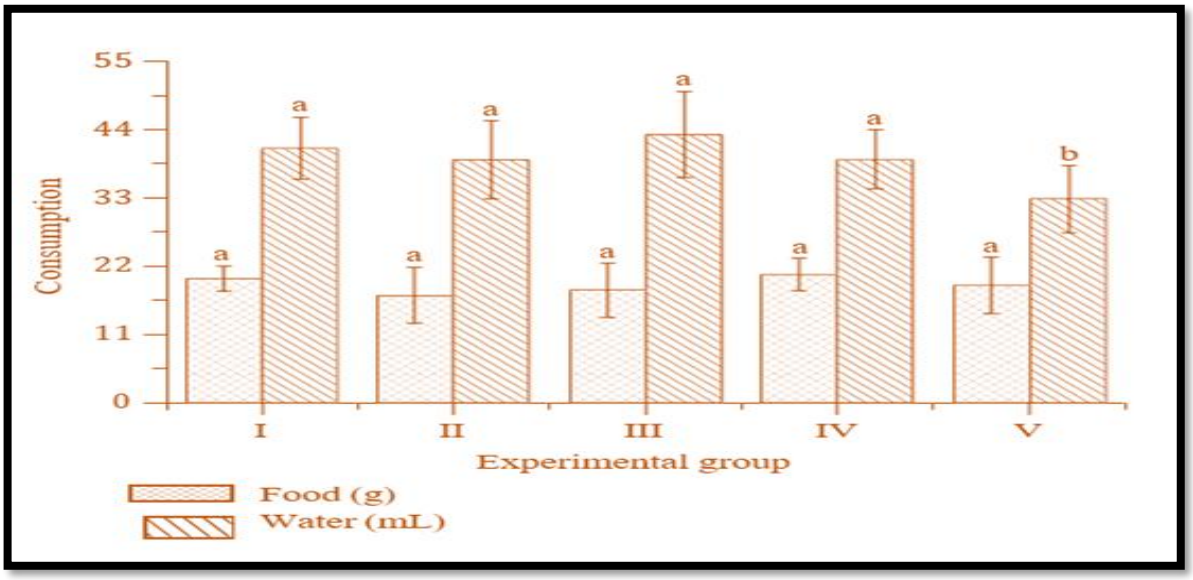

Fig.5 Intake of water and foods for the animals during the experiment. I: control group; II: CCl_4 induced hepatotoxicity group; III: Silymarin treated group; IV and V: *Aloe barbadensis*. Tablets

CONCLUSION

After encapsulation, the Aloe barbadensis material appeared to have a slightly higher moisture content. Because it is hygroscopic, it is plausible that this extract absorbed some moisture while the filling was being done. All of the freeze-dried extract powders of Aloe barbadensis exhibit good flow qualities, with a compressibility index of 11% and a tapped density of 2.96. A drug's bioavailability is greatly affected by its water solubility when administered orally in solid dosage forms. Table 6 shows the results of the solubility testing of the Aloe barbadensis extract, which indicate that the extract is soluble in water. It was concluded that the formulation of *Aloe barbadensis* extract medicinal herb capsules delivery system as an advanced phytotherapy approach for hepatoprotective according to the best results of *in- vitro* dissolution was found to be 89% within 10 minutes in acid medium and were evaluated. The weight gain seen in groups III, IV, and V suggests that even with the presence of CCl4, the administration of tamarind tablets successfully preserved the organic functionality of the biomodels. Both doses of Silymarin and tablets safeguard the biosynthetic function of animals. Conversely, animals in Group II saw a decline in body weight after the fourth day, although having equal food and water intake as the other experimental groups. These findings indicate that the harmful effects of CCl4 resulted in a reduction in biosynthetic activity.

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