Novel Phytosomal Approach for Improving the Therapeutic Performance of Rutin

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ABSTRACT

The present study was aimed at the formulation, optimization, and evaluation of rutin phytosomes to enhance the solubility, stability, and antioxidant activity of rutin. Rutin phytosomes were prepared using different techniques, namely solvent evaporation, salting-out, and lyophilization methods, and comparatively evaluated. Among these methods, the lyophilization technique produced a dry and free-flowing phytosomal complex and was selected for further optimization. The optimized formulation was developed using a three-level factorial design by varying the rutin:SPC ratio and mannitol concentration as independent variables.

The prepared phytosomes were characterized using Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), particle size analysis, zeta potential, and drug content estimation. DSC and FTIR studies confirmed successful complex formation between rutin and phospholipid without any significant chemical incompatibility. The optimized rutin phytosomes exhibited a particle size of 272.6 ± 2.48 nm, PDI of 0.376 ± 0.02, zeta potential of –28.2 ± 0.10 mV, and drug content of 91.38 ± 0.24% w/w. SEM analysis revealed an amorphous and porous morphology, while TEM analysis confirmed the formation of discrete vesicular structures.

The in vitro drug release study demonstrated significantly enhanced and sustained drug release from rutin phytosomes compared to pure rutin, with cumulative release reaching 74.5 ± 0.98% at 24 h. Furthermore, the optimized phytosomes showed slightly improved antioxidant activity in the DPPH assay compared to pure rutin. Overall, the findings indicated that phytosomal encapsulation effectively improved the physicochemical properties and release characteristics of rutin, suggesting its potential for enhanced oral bioavailability and therapeutic efficacy.

Keywords: Rutin, Phytosomes, Soybean Phosphatidylcholine, Lyophilization, Antioxidants

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Introduction:

Rutin is a naturally occurring flavonoid glycoside widely distributed in various medicinal plants, fruits, and vegetables. It possesses several pharmacological activities, including antioxidant, anti-inflammatory, antidiabetic, cardioprotective, and neuroprotective effects. Among these, its potent antioxidant property has attracted considerable attention for the prevention and management of oxidative stress-related disorders. Despite its promising therapeutic potential, the clinical application of rutin is limited due to its poor aqueous solubility, low permeability, and inadequate oral bioavailability. These limitations reduce its absorption and therapeutic effectiveness following oral administration.

Novel drug delivery systems have been explored to overcome the biopharmaceutical limitations associated with phytoconstituents such as rutin. Among these systems, phytosomes have emerged as an effective approach for improving the solubility, stability, membrane permeability, and bioavailability of plant-derived compounds. Phytosomes are phospholipid-based vesicular systems formed by complexation of phytoconstituents with phospholipids, particularly phosphatidylcholine. The formation of a phospholipid complex enhances the lipophilic character of the phytoconstituent and facilitates better absorption across biological membranes.

Soybean phosphatidylcholine (SPC) is commonly used in phytosomal formulations due to its biocompatibility, amphiphilic nature, and ability to form stable vesicular structures. The incorporation of rutin into a phospholipid matrix may enhance its dissolution behavior, gastrointestinal stability, and antioxidant activity. Therefore, the present study was undertaken to formulate and optimize rutin phytosomes using SPC and to evaluate their physicochemical characteristics, drug release behavior, and antioxidant potential.

The prepared rutin phytosomes were characterized using DSC, FTIR, SEM, TEM, particle size analysis, and zeta potential studies. In addition, in vitro drug release and antioxidant activity studies were performed to assess the effectiveness of the developed phytosomal formulation. The study aimed to develop a stable and efficient phytosomal system capable of improving the therapeutic performance of rutin.

Materials and Methods

Rutin was procured from Yucca Enterprises, Mumbai, India. Soybean phosphatidylcholine and Lecithin soya-30% were obtained from Lipoid®, Ludwigshafen, Germany, and HiMedia Laboratories, Mumbai, India, respectively. All chemicals, solvents, and reagents used during the study were of analytical grade

Preparation of Rutin Phytosomes

In the preliminary investigation, rutin phytosomes were prepared using three different techniques, namely solvent evaporation, salting-out, and lyophilization methods, followed by comparative evaluation. The phytosomal complexes were prepared using rutin and soybean phosphatidylcholine (SPC) in a 1:2 molar ratio. Lipoid® S100 was used as the phospholipid source.

Solvent Evaporation Method

Rutin phytosomes were prepared by the solvent evaporation technique according to the method reported by Freag MS et al. Accurately weighed quantities of rutin and SPC in a 1:2 molar ratio were transferred into a 250 mL round-bottom flask containing 20 mL of dioxane:methanol mixture (7:3). The mixture was refluxed at 45 ± 5 °C for 5 h, followed by evaporation of the solvent under reduced pressure using a rotary evaporator. The resulting dried phytosomal complex was collected and stored for further analysis.[1–3]

The dried phytosomal complexes prepared by all three methods were filled into amber-colored glass containers and preserved in a desiccator containing fused calcium chloride at room temperature (20 ± 2 °C) until further use.

Characterization of Rutin Phytosomes

Differential Scanning Calorimetry (DSC)

The thermal characteristics of the rutin:SPC complex were evaluated using differential scanning calorimetry. Samples were sealed in aluminum crimp cells and heated from 25 °C to 500 °C at a heating rate of 10 °C/min under a nitrogen atmosphere maintained at 60 mL/min. Thermograms of pure rutin, SPC (Lipoid® S100), the physical mixture of rutin:SPC (1:2), and rutin phytosomes prepared by solvent evaporation, salting-out, and lyophilization methods were recorded using a thermal analyzer.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectral analysis was carried out to identify potential chemical interactions between rutin and the phospholipid. The attenuated total reflection (ATR) technique was employed, wherein a small quantity of each sample was placed beneath the probe and scanned within the wavenumber range of 4000–500 cm^{-1} using an FTIR spectrometer. The samples analyzed included pure rutin, SPC (Lipoid® S100), the physical mixture of rutin:SPC (1:2), and rutin phytosomes prepared by the lyophilization method.

Selection of Formulation Factors

Based on the results obtained from preliminary phytosome preparation using different methods, the most suitable technique was selected for further optimization. Various formulation variables were investigated, including the selection of suitable co-solvents (methanol, ethanol, chloroform, acetone, and t-butyl alcohol), different types of SPC (Lipoid® S100, Lipoid® S75, Phospholipon® 90G, and Lecithin soya-30%), and varying rutin:SPC ratios (1:1, 1:2, and 1:3).

Formulation of Rutin Phytosomes and Optimization

Rutin phytosomes were prepared by the lyophilization technique with slight modifications to the method described by Freag MS et al. Rutin and SPC were accurately weighed in molar ratios of 1:1, 1:2, and 1:3. Rutin was dissolved in DMSO, while SPC was dissolved separately in t-butyl alcohol. The rutin solution was gradually added to the SPC solution and stirred magnetically for 3 h to facilitate formation of the phytosomal complex.

The prepared phytosomal solution was subsequently subjected to lyophilization using mannitol (0.5–1.5% w/v) as a cryoprotectant. Prior to freeze-drying, the solution was sonicated for 3 min and transferred into vials, which were frozen at –80 °C for 4 h. The frozen samples were then lyophilized at a condenser temperature of –70 °C under a pressure of 40 mbar with a shelf temperature maintained at –40 °C for 24 h, followed by secondary drying at 25 °C for an additional 24 h. The resulting dried rutin phytosomal complex was collected and stored in amber-colored glass containers within a desiccator containing fused calcium chloride until further use.[3]

Design of Experiments (DoE)

Preliminary studies indicated that the drug:phospholipid ratio (w:w) and mannitol concentration (% w/v) were the critical formulation variables influencing phytosomal characteristics. Therefore, a quadratic response surface design based on a second-order polynomial model was employed

to study the effects of these variables on particle size (nm) and drug content (% w/w) using Design Expert® software.

Response Surface Methodology (RSM) was utilized to establish the relationship between formulation variables and responses at different levels. The independent variables, namely drug:phospholipid ratio (A) and mannitol concentration (B), were evaluated at three levels: low (–1), medium (0), and high (+1). A three-level factorial randomized quadratic design consisting of nine experimental runs was employed for optimization studies..[4,5]

The quadratic equation used:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 + \ldots \text{ (Eq. 1)}$$

Where Y is the measured response, b_0 is the intercept, b_1 to b_{22} are regression coefficients, and X_1 and X_2 are coded levels of independent variables.

Independent and dependent variables with coded and actual levels

Factors	–1 (Low)	0 (Medium)	+1 (High)
A = Rutin:SPC ratio (w:w)	1:1	1:2	1:3
B = Mannitol concentration (% w/v)	0.5	1.0	1.5

Dependent variables:

R1 = Particle Size (nm)

R2 = Drug Content (% w/w)

***In Vitro* Evaluation of Optimized Rutin Phytosomes**

Average Particle Size, Polydispersity Index (PDI), and Zeta Potential

The mean particle size (PS) and polydispersity index (PDI) of all prepared formulations, including the optimized batch, were determined using dynamic light scattering (DLS). The zeta potential (ZP) of the optimized phytosomal formulation was measured by electrophoretic light scattering (ELS) using a Malvern Zeta Nano Sizer at a scattering angle of 90° and a temperature of 25 ± 0.5 °C. Prior to analysis, the samples were diluted tenfold with distilled water and sonicated. All measurements were carried out in triplicate.[6]

Drug Content

The amount of rutin entrapped within the phytosomal complex was determined using the spectrophotometric method reported by Tan Q et al. A weighed quantity of phytosomes equivalent to approximately 10 mg of rutin was dispersed in 5 mL of chloroform. In this medium, the phytosomal complex and SPC dissolved, whereas the unentrapped rutin precipitated out. The precipitated rutin was separated by filtration, dried, dissolved in methanol, and analyzed spectrophotometrically at 360 nm.

The percentage incorporated drug was calculated using the following equation:

% Incorporated drug = (W added – W free) / W added × 100

Differential Scanning Calorimetry (DSC)

The thermal behavior of the optimized rutin phytosomes was evaluated under conditions similar to those employed during preliminary characterization studies.

FTIR Spectroscopy

FTIR analysis was performed using the ATR technique to investigate possible interactions between rutin and SPC in the optimized phytosomal formulation. The samples analyzed were the same as those used during the preliminary characterization studies. [7]

Surface Morphology

Scanning Electron Microscopy (SEM)

For SEM analysis, samples of pure rutin and optimized phytosomes were lightly spread over carbon adhesive tape mounted on aluminum stubs. The surface morphology of the samples was then examined and photographed using a scanning electron microscope.

Transmission Electron Microscopy (TEM)

The optimized phytosomal formulation was diluted in a ratio of 1:20 with distilled water and sonicated. A drop of the diluted dispersion was placed onto carbon-coated copper grids and negatively stained using 2% w/w ammonium molybdate solution. The samples were subsequently examined under a transmission electron microscope operated at 200 kV.

***In Vitro* Drug Release**

The in vitro drug release profile of the optimized rutin phytosomes was evaluated using the dialysis bag diffusion technique. Initially, the formulation was placed in pH 1.2 buffer for the first 2 h, followed by transfer into pH 7.4 phosphate buffer for the remaining study period. Samples were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 360 nm.

***In Vitro* Stability**

The stability of optimized rutin phytosomes was evaluated in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4). Approximately 1 mg of phytosomes was dispersed in the respective media and incubated at 37 °C for 2 h in SGF and 6 h in SIF. After incubation, particle size, PDI, and zeta potential were determined. [8-14]

***In Vitro* Antioxidant Activity**

The antioxidant activity of pure rutin, SPC, optimized rutin phytosomes, and standard ascorbic acid was assessed using the DPPH free radical scavenging assay. A 0.1 mM DPPH solution was used, and absorbance was measured at 517 nm. [15]

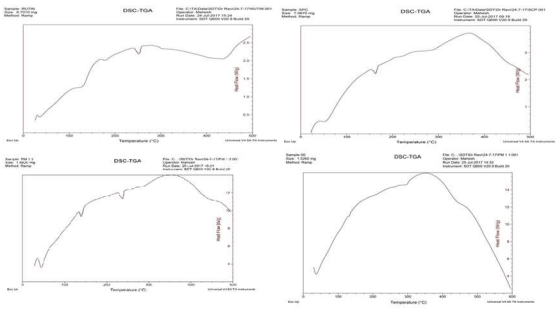
Results and discussion

Preparation of rutin phytosomes

Rutin phytosomes were successfully prepared during the preliminary studies using different preparation techniques. Among the methods evaluated, the lyophilization technique yielded a comparatively dry and free-flowing phytosomal product when compared with the solvent evaporation and salting-out methods. The prepared phytosomes were further characterized by DSC and FTIR studies to obtain preliminary confirmation regarding the complex formation between rutin and SPC.

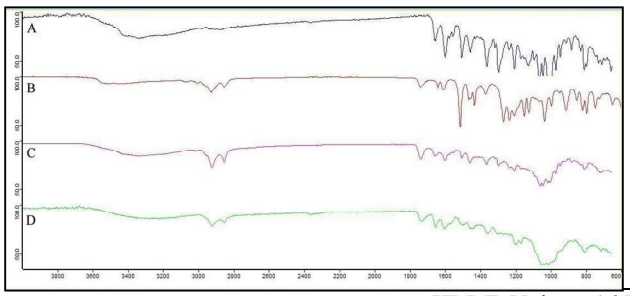
Differential scanning calorimetry(DSC)

The DSC thermograms of pure rutin, SPC, physical mixture of rutin:SPC (1:2), and phytosomes prepared by solvent evaporation are presented in Fig. 1. The thermogram of pure rutin exhibited a sharp endothermic peak at 242 °C, indicating its crystalline



nature. SPC thermogram showed two characteristic endothermic peaks at 68 °C and 165 °C. In the physical mixture of rutin:SPC (1:2), endothermic peaks corresponding to both rutin and SPC were observed; however, these peaks were shifted to lower temperatures, namely 233 °C and 138 °C, respectively. The thermogram of phytosomes prepared by the solvent evaporation method displayed a pattern similar to that of the physical mixture of rutin:SPC (1:2), suggesting partial interaction between rutin and phospholipid components.

Fig 1 DSC thermogram of a) pure rutin b) SPC c) rutin:SPC (1:2) and d) rutin phytosomes prepared by solvent evaporation method.



Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of SPC, physical mixture of rutin:SPC (1:2), and rutin phytosomes prepared by the lyophilization method showed the presence of characteristic peaks corresponding to different functional groups. The characteristic C–H stretching peak of alkane was observed around 2851 cm^{-1} in all samples, indicating retention of the phospholipid structure. The carbonyl (C=O) stretching peak appeared near 1733–1736 cm^{-1}, while the alkene (C=C) stretching peak was observed around 1636–1652 cm^{-1}. Slight shifts in these peaks were noted in the phytosomal formulation compared to SPC and the physical mixture, suggesting possible interactions between rutin and phospholipid molecules. Similarly, peaks corresponding to ether (C–O–C) and phosphoric acid (P=O) groups showed minor variations in the phytosomal complex, indicating successful complex formation. The alkane (C–C) stretching peak also exhibited slight shifting in the phytosomal formulation. Overall, the retention of characteristic peaks along with minor peak shifts confirmed the compatibility of rutin with SPC and the successful formation of rutin phytosomes without any significant chemical incompatibility.

Table 1: Results of FTIR spectroscopy

S.NO	Functional group	Reported frequency (cm^{-1})	Observed Frequency(cm^{-1})		
			SPC	Physical mixture 1:2	Phytosomes 1:2 (by lyophilization method)
1	C-H (Alkane,stretch)	3000-2850	2851.82	2851.52	2851.73
2	C=O (Ketone)	1725-1705	1733.74	1735.99	1732.91
3	C=C (Alkene)	1680-1600	1636.72	1652.64	1652.12
4	C-O-C (Ether)	1300-1000	1264.62	1294.23	1297.73
5	P=O (Phosphoric acid)	1320-1140	1232.92	1231.22	1238.94
6	C–C (Alkane)	1450-1400	1433.09	1425.31	1448.35

Figure 1 : FTIR spectraof rutin (A), SPC (B), physical mixture of rutin:SPC(1:2) (C), and (D) optimized rutin phytosomes

Formulation of Rutin Phytosomes and optimization

Table 2 Three level factorial design

Std	Run	Factor1	Factor2	Response1	Response 2
		A:Rutin: SPC (w:w)	B:Mannitol (%w/v)	Particle Size(nm)	Drug Content (%)
4	1	-1	0	455.1	82.44
9	2	1	1	342.3	82.83
7	3	-1	1	488.2	79.95
3	4	1	-1	323.7	85.62
1	5	-1	-1	472.6	80.65
6	6	1	0	301.4	87.83
2	7	0	-1	286.7	90.18
8	8	0	1	298.5	88.37
5	9	0	0	274.2	93.22

***Invitro* Evaluation of Optimized Rutin Phytosomes**

Average particle size, particle size distribution (PDI) and zeta potential

The particle size (PS) and zeta potential (ZP) values obtained for all rutin phytosomal formulations generated through the Design of Experiments (DoE) software are presented in Table . The optimized rutin phytosomal formulation exhibited a mean particle size of 272.6 ± 2.48 nm, a polydispersity index(PDI)of0.376±0.02,and a zeta potential of –28.2 ± 0.10 mV. These results indicated the formation of a relatively uniform and stable phytosomal dispersion.

Extent of rutin incorporation in rutin phytosomes (drug content)

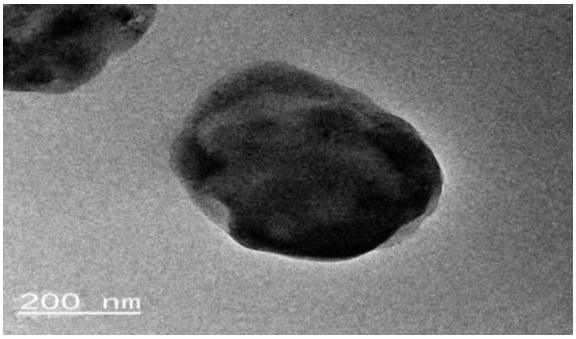
The drug content values of all rutin phytosomal formulations prepared using the DoE approach are presented in Table. The optimized rutin phytosomes showed a rutin incorporation efficiency of 91.38 ± 0.24% w/w, indicating efficient entrapment of rutin within the phospholipid complex.

Surface morphology

Scanning electron microscopy (SEM)

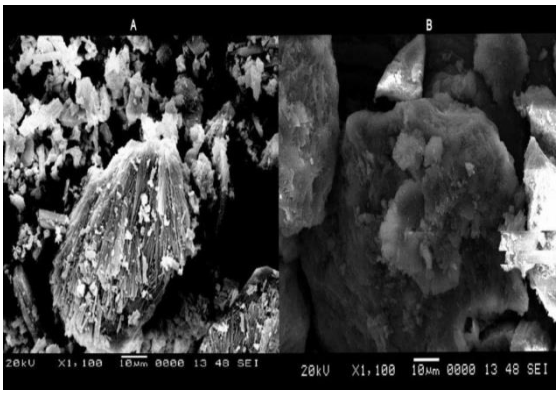
SEM analysis of pure rutin revealed its crystalline nature, characterized by distinct crystalline structures. In contrast, the optimized rutin phytosomes exhibited an amorphous appearance with a fluffy, porous, and rough surface morphology, suggesting successful complex formation between rutin and phospholipid.

Figure 2 SEM analysis of pure rutin



Transmission electron microscopy (TEM) TEM analysis of the optimized rutin phytosomes demonstrated the presence of well-formed and discrete vesicular structures without any visible signs of aggregation or decomposition, confirming the successful formation and stability of the phytosomal vesicles.

Figure3 TEM analysis of pure rutin



***In vitro* drug release**

The in vitro drug release profiles of pure rutin and optimized rutin phytosomes demonstrated a marked difference in the release pattern over 24 h. Pure rutin showed limited drug release, reaching a maximum cumulative release of 34.35 ± 0.85% at 12 h, followed by a gradual decline, which may be attributed to its poor aqueous solubility and instability in the dissolution medium. In contrast, the optimized rutin phytosomes exhibited a sustained and enhanced drug release pattern throughout the study period. The cumulative drug release increased progressively from 9.7 ± 0.22% at 2 h to 74.5 ± 0.98% at 24 h. The improved release behavior of the phytosomal formulation may be due to enhanced solubility, improved dispersion, and better interaction of rutin with the phospholipid matrix. The results indicated that phytosomal encapsulation significantly enhanced the release characteristics of rutin

compared to the pure drug, thereby suggesting improved bioavailability and sustained release properties of the optimized phytosomal formulation.

Table3: Results of In-vitro drug release study

Time(h)	Pure Rutin	Optimized rutin phytosomes
0	0	0
2	10.4±0.08	9.7±0.22
4	18.1±0.72	23.5±1.21
6	24.59±0.53	26.8±1.34
8	29.33±0.86	28.6±1.02
10	33.24±0.22	35.4±1.13
12	34.35±0.85	42.6±1.88
14	33.19±0.39	51.5±1.73
16	30.34±0.99	56.7±1.61
18	28.88±0.62	59.8±1.26
20	26.36±1.17	63.7±2.17
22	23.77±0.77	67.1±1.17
24	19.13±0.96	74.5±0.98

Values are mean±SD(n=6).

In vitro Antioxidant Activity

The antioxidant activity of pure rutin, SPC, optimized rutin phytosomes, and standard ascorbic acid was evaluated using the DPPH free radical scavenging assay at different concentrations ranging from 10–50 µg/mL. Ascorbic acid exhibited the highest antioxidant activity, with percentage inhibition values ranging from 87.02 ± 1.75% to 91.74 ± 1.18%, confirming its potent free radical scavenging ability. Pure rutin demonstrated moderate antioxidant activity, with DPPH inhibition increasing from 25.19 ± 0.62% at 10 µg/mL to 30.30 ± 0.71% at 50 µg/mL. SPC alone showed minimal antioxidant activity, indicating that the phospholipid contributed negligibly to radical scavenging. The optimized rutin phytosomes exhibited slightly higher antioxidant activity compared to pure rutin at all tested concentrations, with percentage inhibition increasing from 25.56±1.84% to 30.75±1.07%. The enhanced antioxidant activity of the phytosomal formulation may be attributed to improved solubility and dispersion of rutin within the phospholipid complex, resulting in better availability of the active constituent for interaction with DPPH radicals. Overall, the results suggested that phytosomal encapsulation retained and slightly enhanced the antioxidant potential of rutin.

Table 4 Percentage inhibition of DPPH by standard (ascorbic acid), pure rutin, SPC, and optimized rutin phytosomes

Concentration (µg/ml)	% Inhibition of DPPH			
	Standard (Ascorbic acid)	Pure rutin	SPC	Optimized rutin phytosomes
10	87.02±1.75	25.19±0.62	4.33±0.99	25.56±1.84
20	87.62±1.82	25.46±1.72	6.89±0.70	25.29±1.23
30	89.16±1.62	25.55±1.24	5.34±0.26	25.92±1.42
40	89.41±0.86	29.58±1.35	6.62±0.38	29.77±0.98
50	91.74±1.18	30.30±0.71	7.23±0.49	30.75±1.07

Values are mean±SD (n=6).

Conclusion

The present study successfully formulated and optimized rutin phytosomes using soybean phosphatidylcholine by the lyophilization technique. Among the different preparation methods evaluated, the lyophilization method produced a stable, dry, and free-flowing phytosomal formulation and was therefore selected for optimization studies. DSC and FTIR analyses confirmed the successful formation of the rutin-phospholipid complex without any significant chemical incompatibility. The optimized rutin phytosomes exhibited suitable physicochemical characteristics, including

optimized rutin phytosomes exhibited slightly enhanced antioxidant activity in comparison with pure rutin, indicating improved availability of the active constituent. Overall, the findings of the study demonstrated that phytosomal encapsulation is a promising strategy for improving the physicochemical properties, release behavior, and therapeutic potential of rutin. The developed rutin phytosomes may serve as an effective delivery system for enhancing the oral bioavailability and pharmacological efficacy of rutin.

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