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FORMULATION AND CHARACTERISATION OF POLYHERBAL SYRUP AGAINST ALDOSE REDUCTASE ENZYME

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ABSTRACT
Background: Traditional medicinal plants have been suggested to help regulate blood glucose levels and inhibit glycation. This investigation aims to formulate and evaluate the potential of herbal formulations containing plant extracts that may inhibit Advanced glycation end product (AGE) formation and provide therapeutic advantages in the management of diabetes. **Methodology:** The herbal syrup containing polyherbal extracts of onion, garlic, and cinnamon was developed at varying concentrations with a viscosity modifier, preservative, flavoring agent, and other excipients. The developed syrup formulations were physicochemically characterised, including antioxidant potential, an ALR (aldose reductase) inhibition assay, and a stability study. **Results and Discussion:** The formulated herbal syrup exhibited a dark brown colour with a slightly Pungent taste. The pH of the syrup was measured at 6.48, indicating a mildly acidic to neutral nature. The viscosity of the prepared herbal syrup formulations (F1–F4) ranged from 3.71 to 3.80 cP. All formulations exhibited concentration-dependent antioxidant activity. F3 demonstrated the highest antioxidant activity and aldose reductase inhibition with 59.58% and 66.44% inhibition at 1000 µg/mL, respectively. Overall, the findings suggest that the herbal syrup formulation exhibited excellent physical and chemical stability over 3 months. **Conclusion:** F3 formulation may be a valuable candidate for the prevention and management of oxidative stress-related disorders, including diabetic complications, owing to its notable aldose reductase enzyme activity and potent antioxidant potential.

INTRODUCTION

Both enzymatic and non-enzymatic processes may induce proteins in the human body to react with sugars, a process known as glycosylation, resulting in the formation of glycoproteins [1]. In contrast, non-enzymatic reactions between Proteins and sugars, referred to as glycation, occur when blood glucose levels remain elevated for extended periods, such as in untreated diabetes. This glycation process results in the development of harmful compounds called Advanced Glycation End Products (AGEs) [2,3], which play an important role in the progression of various diabetic problems [4–6]. Consequently, inhibiting glycation using plant-derived natural compounds has shown promising therapeutic potential in reducing diabetes-related

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complications. Herbal medicinal plants with both antiglycation and antioxidant properties could offer an effective approach to managing diabetes mellitus [7,8]. A study investigated the aldose reductase (AR) inhibitory properties of medicinal plants such as *Allium cepa*, *Allium sativum*, and Cinnamomum zeylanicum. The ethanol extract of these plants exhibited remarkable aldose reductase inhibition. By the Polyol pathway, aldose reductase (AR), which is dependent on NADPH, converts glucose into sorbitol [9]. Under hyperglycemic conditions, an excessive influx of glucose through this pathway can lead to tissue damage via multiple mechanisms. These include the accumulation of sorbitol, resulting in osmotic imbalance [10], dysregulation of the pyridine nucleotide redox state, leading to decreased antioxidant capacity [11], and enhanced AGE formation [12,13]. In diabetes mellitus, the overproduction of sorbitol, which cannot easily diffuse across cell membranes, contributes to intracellular sorbitol buildup. This buildup has been associated with the formation of chronic diabetic problems, for example, cataracts, neuropathy, & retinopathy [14–16]. Diabetic retinopathy (DR), a severe complication of diabetes, occurs when prolonged hyperglycemia causes damage to the retina. The potential of plant-derived phytochemicals to inhibit Aldose reductase (AR) has been extensively researched. These include coumarins, phenolic compounds, flavonoids, and terpenoids. [17]. Among these, polyphenol compounds that effectively trap dicarbonyl species formed during the production of Advanced glycation end products (AGEs), thereby mitigating secondary difficulties of diabetes. Additionally, dietary flavonoids such as quercetin, myricitrin, capillarisin, cirsimaritin, and isorhamnetin-3,7-sulfate have demonstrated significant AR-inhibitory effects [18].

Terpenoids, including diterpenoids like danshenols A and triterpenoids such as 3β,22β-dihydroxyolean-12-en-29-oic acid, maytenfolic acid, triptocalline A, tingenone, tingenin B, and regeol A, have also been reported to suppress AR activity. Similarly, alkaloids such as dehydrocorydaline, isoquinoline, and rhetsinine (N2-(2-methylaminobenzoyl) tetrahydro-1H-pyrido[3,4-b]indol-1-one) have shown promising inhibitory effects against AR [19,20]. Recent studies have indicated that compounds derived from onion, garlic, and cinnamon can inhibit AGE accumulation, offering protective effects against diabetes-related complications in the eyes, kidneys, and vascular system. Moreover, AR expression has been linked to the generation of AGEs, further contributing to diabetic complications [21-23]. Several medicinal plants have demonstrated AR inhibitory properties, making them a safer and potentially more effective alternative to synthetic compounds. Phytochemicals that exhibit both antioxidative and AR inhibitory activities may offer enhanced therapeutic benefits compared to compounds possessing only one of these properties [24]. As interest in natural remedies grows, medicinal plants are once again being explored for the management of diabetes. Notably, Numerous traditional medications have been made from bioactive molecules found in medicinal plants. Since the beginning of time, plants, herbs, and spices have been used as therapeutic agents, highlighting their value as sources of therapeutic compounds [25]. Spices, which include leaves, dried seeds, fruits, barks, or roots, serve as flavoring, coloring, and preservative agents while also offering numerous health benefits. Their medicinal properties have been widely recognized in the prevention and management of conditions like diabetes, cancer, inflammation, and cardiovascular disorders [26,27]. Thus, the goal of this investigation is to determine the effects of selected spices and their phytochemicals on Aldose Reductase, the main regulator of the polyol pathway, to explore their potential role in managing diabetic complications.

MATERIALS AND METHODS

Plant Material

Fresh onion, garlic, and cinnamon were obtained from Sangli, and authentication was done from the Botanical Survey of India (BSI), Pune. A herbarium Specimen was subsequently placed in the Department of Botany, Pune, for future reference.

Plant Extract

The Soxhlet apparatus was used for extraction with 70% ethanol at a 4:1 (v/w) sample-to-solvent ratio. Then centrifuged at 5,000 rpm for 15 minutes. After concentration at 40°C in a rotating evaporator, the resulting extracts were stored. in a freezer. This process was repeated 3 times to ensure thorough extraction. The resulting supernatants were pooled, combined, and concentrated at 40°C in a rotating evaporator, and the extracts were stored. in a freezer until further analysis. Finally, the % yield was calculated.

Formulation of Herbal Syrup

The herbal syrup was formulated in four batches (F1 to F4) with constant amounts of onion extract (75 mg), garlic extract (60 mg), and glycerol (600 mg), and with varying concentrations of Cinnamon and xanthan gum extracts. Cinnamon extract increased from 150 mg (F1) to 300 mg (F4), while xanthan gum

ranged from 30 mg to 45 mg. Propylene glycol was added at 600 mg, and peppermint oil and sodium benzoate were varied to adjust flavor and preserve. Purified water was added to bring the volume to 30 ml to determine the optimal formulation. The formula composition is presented in Table 1.

Table 1: Formulation Batches

Ingredients	Formulation Batches (mg)			
	F1	F2	F3	F4
Onion Extract	75	75	75	75
Garlic Extract	60	60	60	60
Cinnamon Extract	150	300	150	300
Xanthan Gum	30	30	45	45
Glycerol	600	600	600	600
Propylene Glycol	600	600	600	600
Peppermint oil	90	90	90	90
Sodium Benzoate	60	60	60	60
Purified water (for 30 ml)	QS	QS	QS	QS

A precisely weighed amount of xanthan gum was dispersed in 10 ml of purified water and then left to swell at room temperature for 30 min. Sodium benzoate was then mixed with the swollen gum mixture. The mixture was heated to 80°c under continuous stirring for 1 hour to ensure complete dissolution. After heating mixture was left to attain room temperature. The required amount of herbal extracts (onion, garlic, and cinnamon) was added to the cooled solution under constant stirring. A flavoring solution was prepared by dissolving 90 mg of peppermint oil in 600 mg of propylene glycol. This ensured uniform dispersion of the flavor. In a separate mixing vessel, 600 mg of glycerol was added under stirring. The glycerol container was rinsed with purified water, and the rinse was added back to the mixing vessel to minimize material loss. The polyherbal extract solution containing onion, garlic, and cinnamon extracts was gradually added to the mixing vessel under continuous stirring.

The containers used for the polyherbal extracts were rinsed with 5 ml of purified water each, and after rinsing, they were successively transferred to a mixing vessel. Such a rinsing procedure was repeated five times to ensure complete transfer of the extract. The solution was then cooled to 35-40°C. The prepared peppermint oil solution was added to the mixing vessel while stirring. Each container used in preparing the flavoring solution was rinsed with purified water, and the rinsings were added to the vessel to ensure complete recovery of the flavoring agent. Finally, the volume was brought to 30 ml with purified water, and the mixture was stirred to achieve homogeneity.

CHARACTERISATION OF HERBAL SYRUP

Color: A 5 ml sample of syrup was placed in a watch glass, then observed against a white background to assess its color.

Taste: A small amount of the final syrup was sampled by placing it on the tongue.

pH: For pH measurement, A 100 ml volumetric flask was filled with 10 ml of syrup, then distilled water was added to make up to 100 ml. The mixture was then sonicated for 10 minutes, and the pH was determined by using a digital pH meter.

Determination of viscosity

The viscosity of the syrup was determined using the Ostwald viscometer. First, the Ostwald viscometer was carefully cleaned using acetone or warm chromic acid. Then, the viscometer was placed vertically on a suitable stand and filled with water until the liquid in the dry viscometer reached the "G" mark. The time took for water to flow from mark A to mark B was noted. To obtain precise readings, the procedure was repeated at least 3 times, and each repetition was recorded. Afterward, the viscometer was cleaned again and filled with the test liquid (syrup) to the mark A. The time it took for the syrup to flow to mark B was determined. A specific gravity bottle was used to determine the density of both water and syrup.

$$\textit{Formula for viscosity} = \frac{\textit{Density of test liquid} \times \textit{Time required to flow test liquid}}{\textit{Density of Water X Time required to flow water}} \times \textit{Viscosity of water}$$

Antioxidant Potential by DPPH

Total antioxidant activity of the compound was assessed by utilizing the DPPH (1-Diphenyl-2-picryl-hydrazyl) test, and its capacity to scavenge free radicals was assessed. For this, 100 µl of the sample and 100 µl of a 0.1% methanolic DPPH solution were added to a microtiter plate. Afterward, the mixture was incubated in the dark for 30 minutes. After incubation, the samples were examined for color changes: a shift from purple to yellow indicated strong antioxidant activity, whereas a pale pink color suggested weak antioxidant activity. Absorbance was measured using an ELISA plate reader at 490 nm, as described in previous studies [28,29].

ALR inhibition assay

A modified version of the bioassay procedure was followed, as referenced in previous studies [30,31]. To make bioassay solutions, extracts at a concentration of 10 mg/mL were dissolved in DMSO. The reaction mixture had a total volume of

1.0 mL and was prepared at 25 °C. It consisted of 0.7 mL of 50 mM sodium phosphate buffer (pH 6.2), 0.1 mL of lens supernatant enzyme prepared from freshly isolated rat lenses, and 0.1 mL of 10 mM D-galactose as the substrate, with or without 0.5 mL of the plant extract formulation. To start the reaction, 0.1 mL of 0.15 mM NADPH was added, followed by incubation for 45 minutes. After the incubation period, 0.1 mL of 1 M $NaHCO_3$ was added to terminate the reaction. A spectrophotometer was used to detect absorbance at 340 nm. Phosphate buffer (pH 6.2) was used as the negative control, while rutin served as the standard reference [32]. To ensure clarity and consistency, every bioassay was carried out in triplicate. At the end, the inhibitory activity of the extract was calculated using the following formula:

$$\% \, \boldsymbol{ALRI} = \frac{\boldsymbol{Abs\ of\ control - Abs\ of\ Extract}}{\boldsymbol{Abs\ of\ control}}$$

Stability study

The resulting product was tested for pH, viscosity, color, and taste at room temperature to ensure its stability. The study was conducted subsequent to the first, second, and third months following the original analysis.

RESULTS AND DISCUSSION

Numerous studies, including comprehensive reviews of natural aldose reductase inhibitors, have documented that plant-derived phytochemicals—such as flavonoids and polyphenols—possess significant AR-inhibitory and antioxidant activities, lending strong support to our polyherbal strategy with onion, garlic, and cinnamon [34].

%Yield of extract

Table 2 summarises the % yield of all three extracts. Cinnamon extract was found to be the highest 9% among all extracts.

Table 2: % yield of the extracts

Extract	Total Extraction yield	% Yield
Onion Extract	400 mg	8
Garlic Extract	360 mg	7.2
Cinnamon Extract	450 mg	9

General Parameters

The formulated herbal syrup exhibited a dark brown colour with a slightly pungent taste. The pH of the syrup was measured at 6.48, indicating a mildly acidic to neutral nature, which is suitable for oral administration. The general parameters are presented in Table 3.

Table 3: General parameters

Evaluation parameters	Observation
Color	Dark Brown
Taste	Slightly Pungent
pH	6.48

Viscosity

Viscosity is a critical parameter in liquid formulations as it influences pourability, mouthfeel, and overall patient acceptability [33]. The viscosity of the prepared herbal syrup formulations (F1–F4) ranged from 3.71 to 3.80 cP (Table 4), indicating that all formulations exhibited relatively similar flow characteristics. Formulation F3 showed the highest viscosity (3.80 cP), which can be attributed to its higher xanthan gum concentration (45 mg) compared to F1 and F2 (30 mg each). Xanthan gum, being a hydrophilic polymer, effectively increases viscosity by enhancing water-binding capacity. Although F4 also contained 45 mg of xanthan gum, its viscosity (3.75 cP) was slightly lower than F3. Propylene glycol acts as a cosolvent and humectant, affecting the syrup's consistency. The variations in cinnamon extract and xanthan gum across batches had minimal impact on viscosity, suggesting that the primary contributors to rheological behavior were xanthan gum and polyol components (glycerol and propylene glycol). Overall, all formulations demonstrated viscosities within an acceptable range, ensuring ease of administration without compromising stability.

Table 4: Viscosity study of formulation

Parameter	F1	F2	F3	F4
Viscosity (Cp)	3.73	3.71	3.80	3.75

***In vitro* Antioxidant Activity**

Antioxidant activity of the given formulations was assessed using the DPPH method, with ascorbic acid as the standard. The antioxidant potential of the herbal syrup formulations (F1–F4) was evaluated using the DPPH radical scavenging assay, and the results are summarized in Table 5. All formulations exhibited concentration-dependent antioxidant activity, as evidenced by increased % inhibition with rising concentrations (50–1000 µg/mL). Among the formulations, F3 demonstrated the highest antioxidant activity, showing 59.58% inhibition at 1000 µg/mL, which was comparable to the standard ascorbic acid (62.64% inhibition at the same concentration). F2 and F4 also exhibited notable antioxidant activity, achieving 58.98% and 55.59% inhibition, respectively, at 1000 µg/mL, closely approaching that of F3. In contrast, F1 exhibited the lowest antioxidant activity among the formulations, with a maximum inhibition of 48.97%

at 1000 µg/mL. This could be related to its lower concentration of cinnamon extract, peppermint oil, and sodium benzoate compared to other batches. Overall, all formulations exhibited appreciable antioxidant activity, likely due to the combined effects of onion, garlic, and cinnamon extracts, known for their rich phytochemicals, including flavonoids, sulfur compounds, and phenolics. The results suggest that formulation modifications, particularly in cinnamon extract & peppermint oil conc., substantially influenced the antioxidant efficacy. The findings suggest that the formulations, particularly F3, possess notable antioxidant potential.

Table 5: *In Vitro* Antioxidant Activity

Compound (1mg/ml)	**Conc. (**µg/mL)	**Absorbance**	**% Inhibition**
Control		1.858	
Std.Ascorbic acid	1000	0.694	62.64
F1	50	1.403	24.48
	100	1.214	34.66
	250	1.122	39.61
	500	1.008	45.74
	1000	0.948	48.97
F2	50	0.989	46.77
	100	0.887	52.26
	250	0.858	53.82
	500	0.824	55.65
	1000	0.762	58.98
F3	50	1.108	40.36
	100	1.054	43.27
	250	0.938	49.51
	500	0.804	56.72
	1000	0.751	59.58
F4	50	1.126	39.39
	100	1.047	43.64
	250	1.047	43.64
	500	0.983	47.09
	1000	0.825	55.59

Aldose reductase inhibition assay

An aldose reductase enzyme inhibition study assessed the efficacy of herbal formulations (F1 to F4) in inhibiting aldose reductase activity, using rutin as the standard.

The results showed a dose-dependent increase in % inhibition for all formulations. Among them, F3 exhibited the highest inhibition (66.44%) at 1000 µg/mL, closely followed by F4 (65.07%) (Table 6). In comparison, rutin demonstrated a significantly higher inhibition (98.41%) at the same concentration. These findings suggest that F3 & F4 possess promising aldose reductase inhibitory potential, which may help in managing diabetic complications [35]

Table 6: *In vitro* aldose reductase inhibition assay

Groups	**Concentration (µg/mL)**	**Mean OD**	**% Inhibition**
Control	-	0.315	0.00
Standard (Rutin)	200	0.180	42.85
	400	0.120	61.90
	600	0.098	68.88
	800	0.085	73.01
	1000	0.005	98.41
F1	200	0.13	58.73
	400	0.1746	44.57
	600	0.1454	53.84
	800	0.1341	57.42
	1000	0.1267	59.77
F2	200	0.1907	39.46
	400	0.1858	41.01
	600	0.1434	54.47
	800	0.1356	56.95
	1000	0.1242	60.57
F3	200	0.178	43.49
	400	0.1654	47.49
	600	0.1154	63.36
	800	0.1121	64.41
	1000	0.1057	66.44
F4	200	0.1775	43.65
	400	0.1706	45.84
	600	0.155	59.79
	800	0.1345	57.30
	1000	0.110	65.07

The comparative analysis of formulations (F1–F4) indicates that the variations in cinnamon extract and xanthan gum concentrations significantly influenced both the antioxidant and aldose reductase inhibitory activities. The study was designed with two main formulation variables, cinnamon extract (150 mg vs 300 mg) and xanthan gum (30 mg vs 45 mg), and the results reveal interesting compositional relationships. Formulation F3 (150 mg cinnamon + 45 mg xanthan gum) exhibited the highest ALR inhibition (66.44%) and the strongest antioxidant activity (59.58%). This suggests that the higher xanthan gum level (45 mg) improved the solubility, uniform dispersion, and interaction of the phytoconstituents within the assay medium, potentially enhancing their accessibility to the enzyme and reactive radicals. In contrast, although F4 contained more cinnamon extract (300 mg), its performance was slightly lower (65.07% ALR inhibition and 55.59% antioxidant activity).

This could be due to solute saturation or aggregation effects at higher cinnamon concentrations, reducing the effective bioactive fraction available for enzyme inhibition. Moreover, a higher polyphenolic load might slightly increase matrix viscosity or intermolecular interactions, thereby hindering molecular diffusion in vitro. The comparative trends across formulations further support this reasoning: F2 (300 mg cinnamon + 30 mg xanthan) and F3 (150 mg cinnamon + 45 mg xanthan) performed nearly equivalently in antioxidant assays, underscoring the synergistic role of polymer concentration in improving extract performance even at lower cinnamon doses. Therefore, the combination used in F3 appears to provide an optimal physicochemical balance, adequate viscosity for uniform distribution, and sufficient extract concentration for potent bioactivity. Overall, these findings highlight that not merely the amount of cinnamon extract, but the interaction between active phytoconstituents and formulation matrix components (notably xanthan gum) governs biological efficacy. Such formulation–activity correlations should be considered in future optimization to enhance both stability and therapeutic potential.

Stability Study

A 3-month stability study at room temperature was conducted to evaluate the physicochemical stability of the herbal syrup formulations. The parameters assessed included pH, viscosity, colour, and taste (Table 7).

Table 7: 3 months Stability study

Analysis	Initial	1 month	2months	3months
pH	6.48	6.48	6.47	6.51
Viscosity (cp)	3.80	3.80	3.78	3.81
Color	Dark Brown	Dark Brown	Dark Brown	Dark Brown
Taste	Slightly pungent	Slightly pungent	Slightly pungent	Slightly pungent

The pH remained stable throughout the study period, ranging from 6.48 to 6.51, indicating minimal fluctuation and suggesting good formulation buffering capacity. A pH value in this range is favourable for maintaining both ingredient stability and patient acceptability, with no signs of degradation or acidification. The viscosity values demonstrated negligible variation over three months (3.78 to 3.81 cP), indicating that the formulation maintained its rheological consistency without any signs of polymer degradation or phase separation. The slight fluctuation is within acceptable experimental error and does not compromise the product's performance. No change in colour or taste was observed during the stability period. The syrup consistently retained its dark brown colour and slightly pungent taste, indicating that its organoleptic properties remained intact and no sensory deterioration occurred.

Overall, the findings suggest that the herbal syrup formulation exhibited excellent physical and chemical stability over 3 months, maintaining its key quality attributes without noticeable degradation or alteration. These results support the robustness of the formulation for potential long-term storage and commercial viability. These results indicate that the formulation remained stable for three months at room temperature. However, long-term stability studies under accelerated and real-time conditions will be required to establish the formulation's definitive shelf life. The syrup ingredients (onion, garlic, and cinnamon) are natural, widely consumed, and generally regarded as safe, while their therapeutic potential supports further development. With proper standardization, the formulation can be optimized to minimize risks and ensure safe use in diverse populations. Preclinical studies focusing on OECD-guided toxicity assessment, liver and coagulation parameters, and CYP profiling will help establish a strong safety foundation. Clinical translation through Phase I trials with careful dose selection and monitoring of coagulation, liver function, and glucose can pave the way for its safe & effective use in managing diabetes-related complications. The key findings are presented in Table 8.

CONCLUSION

The findings of this study highlight the therapeutic promise of the optimized F3 formulation, comprising onion, garlic, and cinnamon extracts, which exhibited pronounced aldose reductase inhibition and antioxidant activity. Since aldose reductase is a key enzyme in the polyol pathway that contributes to advanced glycation end product (AGE) formation and oxidative stress, its inhibition is of major significance in preventing the progression of diabetes-related complications. By simultaneously suppressing AGE accumulation and enhancing free radical scavenging, the formulation addresses two pivotal mechanisms underlying oxidative stress–induced tissue damage. These results underscore the potential of F3 as a scientifically validated herbal candidate for the management of diabetic complications associated with oxidative stress, while further in vivo and clinical studies are warranted to confirm its broader therapeutic potential. Importantly, this work provides a foundation for advancing polyherbal formulations as effective, stable, and natural alternatives for long-term therapeutic use.

Table 8: Tabular Representation of the summary of key findings

Parameter	Key Findings
Appearance	Dark brown colour
Taste	Slightly pungent taste
pH	6.48 (mildly acidic to neutral)
Viscosity	3.71 – 3.80 cP (across F1–F4 formulations)
Antioxidant activity	All formulations showed concentration-dependent activity; F3 exhibited the highest (59.58% inhibition at 1000 µg/mL)
Aldose reductase (ALR) inhibition	F3 demonstrated maximum inhibition (66.44% at 1000 µg/mL)
Stability	Excellent physical and chemical stability over 3 months
Significance	F3 formulation identified as most promising, with strong antioxidant and ALR inhibitory potential
Potential Applications	May aid in the prevention/management of diabetic complications, neurodegenerative diseases, and cardiovascular conditions

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Sandeep Patil designed the study and planned the work, including its aims and objectives, reviewed the manuscript, and edited the article. Dipak Bhingardeve performed the work, collected data, and wrote the manuscript.

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