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Mechanistic Evaluation of the In vitro Antiviral and Anti-inflammatory Potential of Thyme and Licorice Herbal Preparation

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ABSTRACT

CarvenS™ is a herbal syrup formulated with standardized extracts of Thyme (*Thymus vulgaris* L., Lamiaceae, herba) and Licorice (*Glycyrrhiza glabra* L. root, Fabaceae) in a *Stevia* sp.-base, commonly used in Türkiye for the relief of cough, cold, and flu symptoms. This study assessed its in vitro inhibitory potential against angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), neuraminidase (NA), and selected pro-inflammatory mediators including tumor necrosis factor-alpha (TNF-α), cyclooxygenase (COX), and lipoxygenase (LOX), respectively. In addition, the phytochemical profile was determined using high-performance liquid chromatography (HPLC), which revealed the presence of 1.07%(w/v) rosmarinic acid and 0.4 %(w/v) glycyrrhizic acid. Enzyme inhibition assays were performed on a microplate system using commercial kits at a final concentration of 20 µg/mL. The syrup showed strong inhibitory effects on ACE2 (81%), TMPRSS2 (89%), and NA (85%). Anti-inflammatory activity was also evident, with inhibition of TNF-α (74.2%), COX-1 (76.3%), COX-2 (78.9%), and 5-LOX (83.1%), respectively. As an overall conclusion, the experimental findings indicate that CarvenS™ demonstrates substantial enzyme inhibitory activity relevant to both antiviral and anti-inflammatory pathways. Further in vivo studies are needed to validate these results and clarify the underlying mechanisms.

Introduction

Seasonal influenza and the common cold (acute upper respiratory infection) are associated with significant morbidity and potential complications, which have prompted the long-standing use of various therapeutic approaches, including both herbal and conventional medicines[1,2]. In particular, the excessive use of antibiotics in children has raised concerns due to adverse side effects, encouraging a shift towards the utilization of medicinal plants as alternative therapeutic approaches, especially for post-viral acute cough[3]. Cough is a non-life-threatening but irritating symptom commonly triggered by viral or bacterial infections. It poses a significant discomfort, particularly for children and adolescents. To address this, over the counter (OTC) cough remedies are widely used, with a growing preference for those formulated with licensed herbal ingredients[4,5]. For many years, a variety of herbal medicines were formulated for cough and common cold, using a wide range of plant species. Among the most commonly utilized medicinal plants are *Thymus vulgaris* L. (common thyme- Lamiaceae), and *Glycyrrhiza glabra* L. (licorice - Fabaceae), each recognized for their therapeutic properties of their relevant preparations in traditional medicine[5,6].

In addition to its culinary applications, *T. vulgaris* preparations were long valued for its traditional medicinal properties, including its antibacterial[7], antitussive[8], antispasmodic, and anti-inflammatory effects[9]. Particularly in the Mediterranean region, thyme is highly regarded for its versatile uses. It was commonly administered to patients in the form of teas (infusions), syrups, and ointments[10]. Previous studies demonstrated that *T. vulgaris* has antifungal[11], antiviral[12], antibacterial[13], antioxidant, antitumor[14], and anti-inflammatory[15] activities. The essential oil of *T. vulgaris* is rich in various bioactive compounds, with key components including thymol, p-cymene, 1,8-cineole, γ-terpinene, and carvacrol. These compounds are largely responsible for the plant's medicinal effects[16].

G. glabra was traditionally utilized in various preraparations in the treatment of various ailments, including respiratory disorders, stomach ulcers, colic, cough, and rheumatism[17]. Additionally, it was

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long served as a valuable ingredient in the food industry due to its thermally stable sweetening properties, particularly in herbal teas and other formulations[18]. Previous research was demonstrated that licorice possesses a wide range of pharmacological properties, including antitussive, expectorant[19], anti-ulcer[20], anti-inflammatory[21], antibacterial[22,23], antiviral[22,24], antiallergic[25], and anticancer[26] activities. Additionally, *G. glabra* has been traditionally employed for its immune-boosting effects over an extended period[27].

The aim of this study was to determine the presence and quantitative levels of rosmarinic acid and glycyrrhizin in the commercial product CarvenS™ by EnaFarma. In addition, the aim of the study is to elucidate the enzymatic mechanisms underlying the anti-inflammatory and antiviral effects of a standard product combined with two important herbal extracts with known traditional use.

Results

HPLC Analysis

Quantitative analysis of rosmarinic acid and glycyrrhizin in CarvenS™ was performed using the HPLC method. Since the herbal product contains *Thymus vulgaris* and *Glycyrrhiza glabra*, rosmarinic acid and glycyrrhizin were used as reference compounds. Figure 1 presents the HPLC chromatograms of rosmarinic acid and glycyrrhizin, respectively.

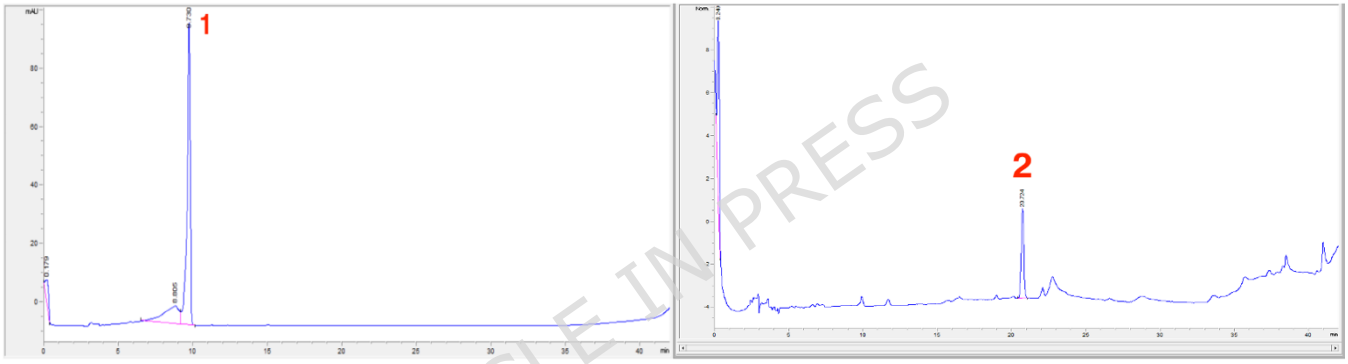


Figure 1. HPLC chromatogram of rosmarinic acid and glycyrrhizin at 330 nm and 280 nm, respectively (1: rosmarinic acid tR: 9.730; 2: glycyrrhizin tR: 20.724).

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As shown in Figure 2, rosmarinic acid was the main component of the syrup, while glycyrrhizin was also identified as a constituent (Figure 3).

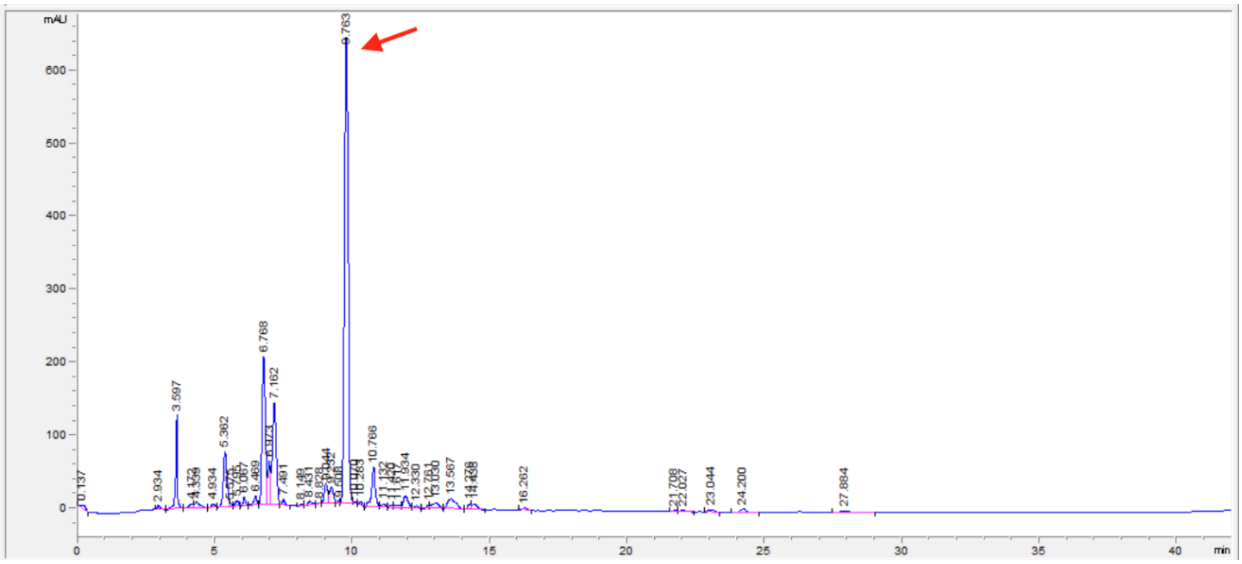


Figure 2. HPLC chromatogram of the CarvenS™ (Rosmarinic acid tR: 9.763) at 330 nm.

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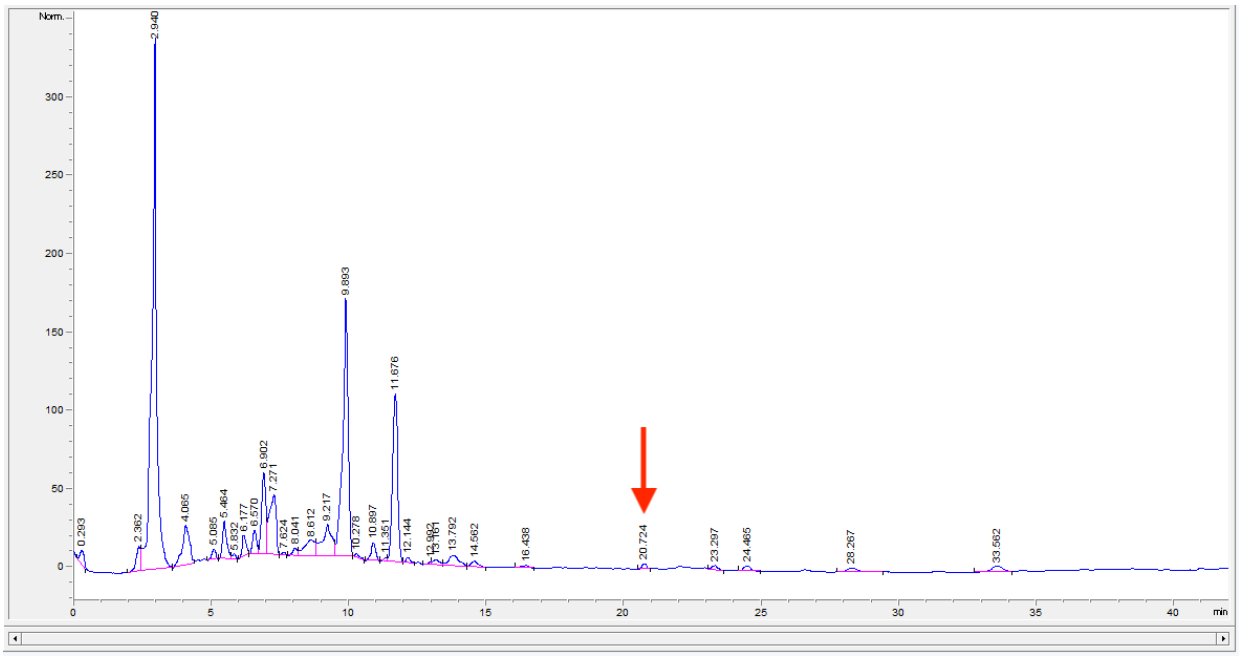
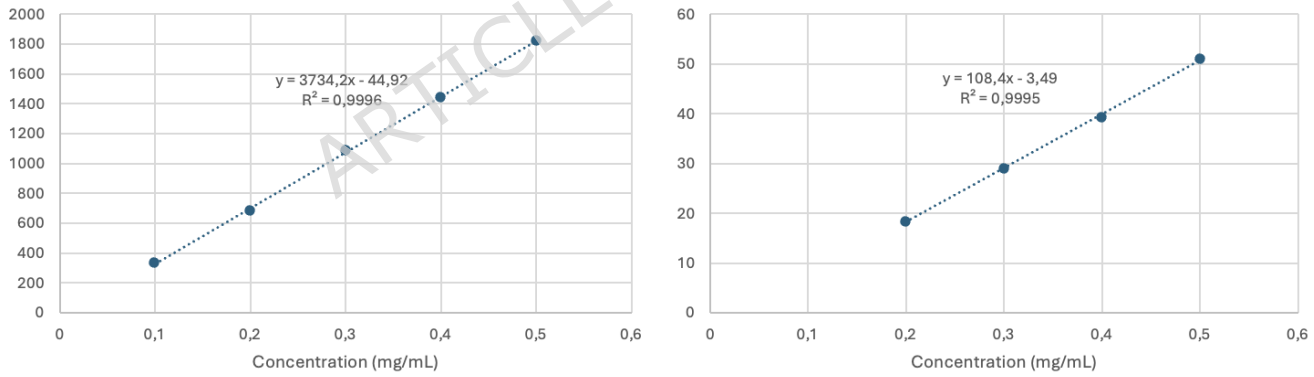


Figure 3. HPLC chromatogram of the CarvenS^{TM} (Glycyrrhizin tR: 20.724) at 280 nm.

According to the quantitative results which were calculated by using the calibration curves given as Figure 4, the rosmarinic acid content of the extract was determined as 1.07% (w/v), and the glycyrrhizin content was determined as 0.4% (w/v).

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(a) (b)

Figure 4. Calibration curves of the standards: (a) rosmarinic acid; (b) glycyrrhizin (n = 3).

Antiviral and Anti-inflammatory Activities

In the present study, the in vitro angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), and neuraminidase (NA) enzyme inhibitory activities of the CarvenS^{TM} (at a concentration of 20 µg/mL) were evaluated by enzyme assay kits, respectively. The results of the study showed that CarvenS^{TM} syrup inhibited the ACE2 enzyme by 81% at tested concentration. Inhibitory effects on NA and TMPRSS2 were determined as 85% and 89%, respectively (Table 1).

CarvenS^{TM} was tested using commercial enzyme inhibition assay kits to evaluate its anti-inflammatory activity against tumor necrosis factor-alpha (TNF-α), and cyclooxygenase (COX) enzymes. The TNF-α inhibition potential of the syrup was calculated as 74.2%, while the in vitro COX-1 and COX-2 inhibition rates were found to be 76.3% and 78.9%, respectively.

The 5-lipoxygenase (LOX) enzyme inhibitory potential of CarvenS^{TM} was evaluated using an in-house spectroscopic method, by using nordihydroguaiaretic acid as the positive control. The results

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revealed that CarvenS™ inhibited the 5-LOX enzyme by 83.1% (Table 1).

Assays	Test Results (%)
ACE2[a]	81 ± 0.73
Standard (kit)	99.9 ± 0.1
NA[b]	85 ± 0.45
Standard (kit)	99.1 ± 0.12
TMPRSS2[c]	89 ± 0.52
Standard (kit)	99.7 ± 0.2
TNF-[d]	74.2 ± 0.65
Standard (kit)	99.4 ± 0.17
COX-1[e]	76.3 ± 0.84
Nordihydroguaiaretic acid[6]	98.3 ± 0.21
COX-2[f]	78.9 ± 0.92
Nordihydroguaiaretic acid	95.8 ± 0.27
5-LOX[g]	83.1 ± 0.76
Nordihydroguaiaretic acid	99.2 ± 0.

Table 1. The results of the enzyme inhibitory activity assays. Data are presented as mean ± SD (a: angiotensin II converting enzyme, b: neuraminiadase, c: transmembrane protease serine 2, d: tumor necrosis factor-, e: cyclooxygenase-1, f: cyclooxygenase-2, g: 5-lipooxygenase)

Discussion

The phytochemical composition of *T. vulgaris* and *G. glabra* extracts has been previously characterized, and the findings of the present study are consistent with earlier reports. Specifically, the major component of *T. vulgaris* was consistent with previous studies[28-30], including the findings of Lagouri and Nisteropoulou, who reported that *T. vulgaris* contained the highest amount of rosmarinic acid (4,532 mg/kg, dry weight) among *Origanum onites* and *O. basilicum*[30]. Likewise, glycyrrhizin was identified as the principal compound in *G. glabra*, with concentration levels ranging from 0.177% to 0.688% (w/w) of the dried material, as reported by Basar et al[31].These results validate the presence of bioactive markers and support the selection of reference compounds used in the analytical evaluation of CarvenS™. However, we acknowledge that attributing the potent biological activity solely to these markers would be speculative without isolation experiments; therefore, the observed effects are likely the result of synergistic interactions between these major constituents and the complex phytochemical matrix.

In the enzyme inhibition assays, CarvenS™ at the concentration of 20 µg/mL demonstrated significant activity, particularly against TMPRSS2 (89%) and NA (85%), while its effect on ACE2 was comparatively lower (81%). This selectivity may have therapeutic relevance, as both TMPRSS2 and NA are essential for the entry and spread of influenza viruses within host cells. The inhibition rates observed in this study highlight the potential of CarvenS™ in targeting viral entry mechanisms. Moreover, the traditional medicinal use of *T. vulgaris* and *G. glabra* in treating respiratory infections such as flu and the common cold is well documented[32,33], and our findings offer scientific support for these ethnobotanical applications. However, it is important to note that 20 µg/mL is an experimental concentration used here for mechanism identification, and future pharmacokinetic studies are required to determine the achievable tissue concentrations in humans.

The significance of ACE2 as a viral entry receptor for SARS-CoV-2 has been widely discussed in recent literature[34]. The interaction between the viral spike protein and ACE2 is a critical step for infection, and several therapeutic strategies aim to disrupt this binding, including monoclonal antibodies and recombinant human ACE2 (rhuACE2)[35]. Based on Yao et al.'s findings, the aqueous and ethanolic extracts of *T. vulgaris* exhibited strong ACE2 inhibitory activity, reducing enzyme activity by approximately 82.6% and 86.4%, respectively, at a concentration of 3.3 mg/mL, which is in agreement with our results[36]. Given that CarvenS™ inhibited ACE2 in vitro, the product and its key phytoconstituents may exhibit additional antiviral effects beyond influenza. Earlier investigations have already demonstrated the potential of *T. vulgaris* against coronaviruses[37], further reinforcing this assumption.

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Apart from antiviral activity, both *Thymus* and *Glycyrrhiza* species are recognized for their antimicrobial properties against a wide range of human pathogens[38,39], as well as their documented antiviral capacities[40,41]. However, to date, no published study has explored the antiviral potential of a combined formulation of these two plants. To the best of our knowledge, this is the first investigation examining the inhibitory effects of a commercial syrup containing both *T. vulgaris* and *G. glabra*, targeting the ACE2, TMPRSS2, and neuraminidase enzymes associated with influenza virus pathogenesis.

In addition to antiviral effects, CarvenS™ also demonstrated anti-inflammatory potential. Prior studies suggest that *T. vulgaris* exerts selective inhibition on COX-1[42, 43], while *G. glabra* has well-documented anti-inflammatory properties through various mechanisms[43, 44]. The present study expands on these findings by evaluating the biological activity of their combination, revealing notable and selective inhibition of both COX-1 (76.3%) and COX-2 (78.9%) enzymes.

The experimental findings of this research study emphasize the pharmacological relevance of combining *T. vulgaris* and *G. glabra* in a single formulation. The observed enzyme inhibition profiles provide a basis for further investigation into the therapeutic potential of such combinations, especially in the context of viral respiratory infections. The proprietary medicinal product CarvenS™, which has been used for more than a decade, is a special blend of *T. vulgaris* and *G. glabra* which may be used both for the prevention and treatment against coronaviruses, among other microorganisms.

The findings of this study indicate the need for comprehensive in vivo and preclinical investigations to elucidate the underlying mechanisms and assess their translational potential. Further bioassays and clinical evaluations are also required to substantiate the observed anti-SARS-CoV-2 activity.

Conclusion

This study provides the first scientific evidence on the combined antiviral and anti-inflammatory potential of *T. vulgaris* and *G. glabra* extracts formulated in the commercial product CarvenS™. The extract exhibited notable inhibitory effects against key viral enzymes (TMPRSS2, NA, and ACE2) alongside COX-1 and COX-2 inhibition, supporting its traditional use in respiratory tract infections. The consistency of our phytochemical findings with previous literature further validates the analytical approach and selection of reference compounds. Overall, these results highlight the pharmacological relevance of combining *T. vulgaris* and *G. glabra* in a single formulation. It should be noted that this study utilized a fixed-concentration screening approach (20 µg/mL) to identify molecular targets. While this demonstrated high inhibitory potential (>74%) comparable to positive controls, full dose-response curves (IC_{50}) were not established due to the methodological design of the commercial kits. Thus, the results should be interpreted as a qualitative confirmation of the mechanism rather than a quantitative potency analysis. Consequently, future research should include comprehensive *in vivo*, preclinical, and clinical studies to confirm the therapeutic potential and elucidate the underlying mechanisms of action against viral respiratory pathogens, including SARS-CoV-2.

Methods

Commercial standardized and deodorized extracts of *Thymus vulgaris* L. and *Glycyrrhiza glabra* L. (CarvenS™, EnaFarma) from MartinBauer, formulated in a *Stevia* sp.-based, diabetic-friendly syrup (Batch No: 21001, EnaFarma, Istanbul, Türkiye).

HPLC Studies

The HPLC analysis was performed using an Agilent 1100 HPLC system equipped with a UV-DAD detector. Standard solutions of analytical-grade rosmarinic acid and glycyrrhizin, purchased from Sigma Aldrich (Steinheim, Germany) were prepared in ethanol at a concentration of 10 mg/mL and filtered through a 0.22 µm membrane filter. CarvenS™ was dissolved in water and ethanol, at a concentration of 100 µL/mL. The validated method described by Okur et al.[45] was followed for the separation, using a C18 column (250 x 4.6 mm, 5 µm particle size). The mobile phases consisted of Phase A (acetonitrile: distilled water: formic acid, 10:89:1, v/v) and Phase B (acetonitrile: distilled water: formic acid, 89:10:1, v/v), with a gradient elution. The proportion of Phase B increased from 15% to 100% over 40 minutes. The flow rate was maintained at 1.0 mL/min, with triplicate injections for all samples. Detection was performed at 330 nm for rosmarinic acid and CarvenS™; 280 nm for glycyrrhizin. The injection volume was 20 µL, and the column temperature was held at 40°C

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throughout the analysis.

Sample Preparation

Before the assays, the CarvenS™ syrup was diluted with the respective assay buffer to reach the final concentration of 20 µg/mL. This step ensured that the pH and ionic environment were optimal for enzymatic activity and minimized potential physicochemical interference from the syrup matrix.

Antiviral Activity

The standard protocols of the enzyme assay kit ("ACE2 Inhibitor Screening", "Neuraminiadase (NA)", "TMPRSS2 Fluorogenic") were followed. Stock solutions of the test substances were prepared in DMSO (1%, v/v) and aliquots of CarvenS™ (20 µg/mL) was transferred to each well. The enzyme solution was added to all wells except the blank, followed by the addition of the substrate solution (40 µL) to each well. The enzyme re-action was measured in a SpectraMaxi3 microplate reader (Molecular Devices, CA) in fluorescence mode after incubation for 30 min at 37°C. The microplate reader was set at Ex/Em and UV/visible wavelengths specific for each enzyme assay according to the kit protocol. To rule out potential false-positive results caused by fluorescence quenching or intrinsic autofluorescence of the extract, sample blanks (containing the test sample and buffer without the enzyme) were analyzed in parallel, and these background values were subtracted from the experimental readings. Camostat (BPS Bioscience, 78083, San Diego, CA) was used as a positive control for TMPRSS2 assays. Other positive control substances cannot be named because they are not clearly stated in the kit content[46].

Anti-inflammatory Activity

COX-1/COX-2 Enzyme Inhibitory Assay

The CarvenS™ was tested using a commercial COX-1 (Ovine), COX-2 (Human recombinant), and fluorometric inhibitory screening assay kit following the instructions recommended by the manufacturer (Cayman test kit 700100, Cayman Chemical Company, Ann Arbor, MI, USA). Briefly, 150 µL of assay buffer (0.1 M Tris-HCl pH 8.0), 10 µL of Heme, 10 µL of enzyme (COX-1 or COX-2), and 10 µL of the test sample were added to the wells. After 5 min at 25 °C, 10 µL of ADHP (10-acetyl-3 7-dihydroxy phenoxazine) and 10 µL of arachidonic acid were added to initiate the reaction. The plate was incubated at room temperature for 2 min followed by fluorescence measured at 530 nm (excitation) and 585 nm (emission). Appropriate sample blanks were utilized to correct for any non-specific fluorescence interference arising from the complex syrup matrix. The triplicate experimental data are expressed as mean ± standard deviation (SD)[47].

5-LOX Enzyme Inhibitory Assay

The CarvenS™ was tested using an in-house assay, where reaction was initiated by adding linoleic acid solution and the absorbance was measured at 234 nm for 10 min in a spectrophotometer. Sample blanks containing the extract without the substrate were used to eliminate the intrinsic absorbance of the formulation. The maximum concentration of the CarvenS™ was 20 µg/mL. The enzyme activity was calculated as the amount of product formed per minute of the reaction for controls (without inhibitor) and test samples. Nordihydroguaiaretic acid (NDGA) was used as a positive control. All experiments were performed in triplicate and the results were reported according to standards described in the literature[47].

Statistical Analysis

The statistical analysis was carried out using GraphPad Prism, v7.02 (GraphPad, La Jolla, CA). The data were expressed as the mean with standard deviation. The value of $p < 0.05$ was accepted as statistically significant.

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Author contributions statement

Conceptualization, A.E.K, R.B. and F.D.; methodology, A.E.K, R.B. and F.D; software, A.E.K, R.B. and F.D; validation, A.E.K, R.B.; formal analysis, A.E.K, R.B.; investigation, A.E.K, R.B. and F.D; resources, A.E.K, R.B. and F.D; data curation, A.E.K, R.B.; writing—original draft preparation, A.E.K, R.B.; writing—review and editing, F.D..; visualization, A.E.K, R.B. and F.D; supervision, F.D. All authors have read and agreed to the published version of the manuscript.

Additional information

Competing interests

The authors declare no competing interests.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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