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Antiviral Activity of *Crataegus azarolus* Extract Against Herpes Simplex Virus Type 1

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Abstract

Background: due to the spread of infections caused by the herpes simplex virus and the occurrence of antiviral resistance, many studies are conducted to obtain alternative treatments with better performance and fewer side effects. This research was carried out to measure the phenolic and flavonoid content of extracts obtained from Crataegus azarolus (C. azarolus) leaves and flowers and to investigate the antiviral effect of this plant on herpes simplex virus type 1 in cell culture. Methods: In this study, the phenolic and flavonoid content of extracts received from hawthorn leaves and flowers was measured using a Cary 300 UV-Vis spectrometer. The MTT technique was used to examine the toxicity of C. azarolus extract in Vero cells. The effect of the extract against herpes simplex virus type 1 (HSV-1) was then tested at various concentrations. Results: Compared to the flower extract, C. azarolus leaf extract has a much higher total phenolic and flavonoid content. The fifty percent cytotoxic for C. azarolus leaf and flower extracts was 1203 and 870 g/ml, respectively. Flower and leaf extracts were revealed to have antiviral activities of 9.50 and 10.41, respectively. Conclusion: The active components in hawthorn leaf extract help minimize the replication of herpes simplex virus type 1.

Keywords: Anti-virus; Cytotoxic; Herbal medicine; Hawthorn; Vero cells.

INTRODUCTION

Throughout history, viruses have infiltrated all aspects of human life, and everyone is inevitably exposed to viral infectious diseases (Tapper 2006; Iversen 2018). Herpes simplex virus is one of the prevalent members of the Herpesviridae family of viruses (Saleh et al. 2021; Saranathan et al. 2022). HSV-1 and HSV-2 are two serotypes of this highly infectious virus that can cause significant infections and other complications (Backes et al. 2022). HSV type 1 (HSV-1) can be transmitted through close contact with infected saliva. This virus can be responsible for various severe local symptoms such as herpes lesions, inflammation, and ulcers on the facial skin, oral cavity, or lips. In addition, it can lead to herpetic stromal keratitis, HSV-1 encephalitis, and herpetic gingivostomatitis (Koujah et al. 2019; Gavanji 2022). Herpes infections can be treated using a variety of approaches, including physical methods, management strategies, and antiviral medications (Gavanji et al. 2012). Antiviral drugs have become crucial in the management of HSV and the amelioration of herpes symptoms (Gavanji 2013). Acyclovir is currently the most commonly used antiviral medication for treating herpes infections (Modi et al. 2008). Other antiviral drugs, such as Penciclovir, Valaciclovir, Cidofovir, and Famciclovir, are administered to inhibit herpes simplex virus replication by inactivating viral DNA polymerase (Shiraki 2018; Gavanji et al. 2015). Antiviral resistance, resulting from mutations in the viral DNA polymerase gene, is a growing concern in herpes therapy (Bestman-Smith and Boivin 2003). Therefore, the development of novel antiviral medications remains a priority in many countries. Plants contain alkaloids, flavonoids, phenols, and other bioactive compounds that have demonstrated antiviral effects against a wide range of viruses, including HSV (Gavanji et al. 2014; van de Sand et al. 2021). Different parts of Crataegus azarolus (C. azarolus), a member of the Rosaceae family, possess antioxidant, antidiabetic, antimicrobial, antiviral, anti-inflammatory, antithrombotic, hypolipidemic, cardioprotective, hepatoprotective, and antihypertensive activities (Abu-Gharbieh and Shehab 2017; Kumar et al. 2012). These properties have led to the use of this plant in traditional medicine for the treatment of various disorders such as asthma, insomnia, influenza, cough, bronchitis, headache, respiratory and reproductive disorders, and cardiovascular diseases (Kumar et al. 2012; Hanus et al. 2004). However, there is limited evidence regarding the antiviral effects of this plant.

Therefore, this study aimed to investigate the in vitro antiviral activity of different concentrations of C. azarolus flower and leaf extracts against HSV type 1.

MATERIALS AND METHODS

Plant collection and extraction

Flowers and leaves of *C. azarolus* were collected from Kohgiluyeh and Boyer-Ahmad province, Iran, which were approved by the Herbarium Department of Traditional Medicine Research Institute. Samples were dried in the shade under sterile conditions and ground into a powder by a grinder. Extraction was done by the maceration method. Briefly, flower and leaf powders were immersed in 70% ethyl alcohol for 96 hours on an orbital shaker at 160 rpm at room temperature and then filtered. The obtained extracts were concentrated using a rotary evaporator at a temperature of 40°C under a vacuum. The extracts were dissolved in Dimethyl sulfoxide (DMSO) 10% to a final concentration of 10 mg/mL and kept at 4°C (Sabouri Ghannad et al. 2014).

Determination of total phenolic

Total phenolic content in flowers and leaves was measured using Folin-Ciocalteu reagent by a Cary 300 UV-Vis spectrometer. For this purpose, 1 mg/ml of flower or leaf extract was dissolved in 60% methanol. Then, 0.5 ml of Folin-Ciocalteu reagent (FCR) was added to 0.1 ml of the extract and kept at room temperature for 7 minutes. For this purpose, 1 mg/ml of flower or leaf extract was dissolved in 60% methanol. Then, 0.5 ml of Folin-Ciocalteu reagent (FCR) was added to 0.1 ml of the extract and kept at room temperature for 7 minutes. Later, 0.4 ml sodium carbonate (7.5% w/v) was added. After one hour, the absorbance of the samples was read by a spectrophotometer in three repetitions against a blank. Gallic acid was used as a standard to draw the calibration curve. The total phenolic content was reported based on mg of GAE/g of extract powder.

Determination of total flavonoid

The total flavonoid content of flowers and leaves was determined using the aluminum chloride colorimetric method. To achieve a final concentration of 1.0 mg/mL, C. azarolus extract was diluted in methanol, and 0.5 mL of each sample was added to 1.5 ml of methanol, 0.1 ml of 10% aluminum chloride, 0.1 ml of 1M potassium acetate, and 2.8 ml of distilled water. Then the solutions were placed at room temperature for 30 minutes and the absorbance of the solutions was measured at 415 nm in three repetitions using a spectrophotometer. The total flavonoid content was reported based on mg RE/g of extract powder.

Cells and viruses

African green monkey kidney (Vero) and herpes simplex virus type 1 cells were obtained from the Traditional Medicine Research Institute to examine the antiviral activities of *C. azarolus* extract. Vero cells were cultured in MEM or Eagle's minimum essential medium containing 10% newborn calf serum (NCS), 100 U/ml penicillin (Gibco), and 100 µg/ml streptomycin sulfate (Gibco) (Gavanji et al. 2026).

Cytotoxicity assay determination using the MTT assay

The cytotoxic effect of flower and leaf extracts was examined by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. This procedure relies on the mitochondrial succinate dehydrogenase enzyme in live cells, which changes the yellow MTT solution into purple formazan crystals. These insoluble crystals can be dissolved in a suitable solvent such as DMSO and then measured by ELISA (Gavanji et al. 2014). In each well of the 96-well plate, 180 microliters of cell suspension (Vero cells), equivalent to 3×10^4 cells, were poured. Then, the extracts were added at different concentrations (400 to 1500 µg/ml). The antiviral drug acyclovir was regarded as a positive control, while the culture medium containing 0.5% DMSO without extract was used as a negative control. The plate was incubated for 48 hours at 37°C in an incubator with 5% CO_2. Then 20 µl of MTT solution was added to each well and incubated for 2 hours. The wells were filled with 100 µl of DMSO and thoroughly mixed to dissolve the formazan crystals. Using an ELISA device, the absorbance of MTT at 560 nm was measured. The following formula was used to compute the proportion of survived cells, but 100 was considered for both the positive and negative control groups. A concentration of the tested compounds that reduces the percentage of cell viability by half was considered CC_{50} (Gavanji et al. 2023; Gavanji et al. 2024)

Percentage of cell survival =

$$\left[\frac{\text{Test compound } \mathbf{OD} - \text{Blank } \mathbf{OD}}{\text{Negative control}\mathbf{OD} - \text{Blank } \mathbf{OD}}\right] \times 100$$

Antiviral activity

A plaque reduction test on Vero cells was performed to examine the anti-herpes virus type 1 activity of *C. azarolus* flower and leaf extract. Plaque reduction is a sensitive and accurate test that may be performed to determine the effect of a compound on the number of plaque-forming units (PFU) compared to the control. First, in each well of a 24-well plate, 400 × 103 µl of Vero cells were cultured in 1 ml of DMEM containing 3% inactivated FBS and incubated for 24 hours. After this time, 1 µl of melted viral suspension was added.

After one hour, the culture medium was removed and washed cells with 1 ml of preheated DMEM medium. To each well, 20 µl of various extract concentrations were added along with 2 ml of preheated DMEM medium with methylcellulose. The control wells received 20 µl of acyclovir as a positive control and 20 µl of DMSO diluted with double distilled deionized water as a negative control and incubated for 48 hours. The number of plaques observed per well and the inhibition rate of each extract at different concentrations were determined using the following formula:

Percentage of inhibition =

$$[1 - \frac{(\text{number of plaque}) \text{ tested}}{\text{Number of control plaque}}] \times 100$$

Data analysis

One-way ANOVA was used to analyze the cytotoxicity and Anti-HSV-1 activity using GraphPad Prism 6 software (GraphPad Software, La Jolla, CA, USA). Tukey's multiple comparison tests were used to compare means. Phenolic and flavonoid contents in each extract of C. azarolus were assessed using an independent sample t-test. P-values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

The results of the present study showed that the total phenolic and flavonoid content in C. azarolus leaf extract is significantly higher than in its flower extract ($p < 0.05$, Figure.1).

The cytotoxicity test of *C. azarolus* leaf and flower extracts exhibited that cell viability significantly reduced with increasing extract concentrations (Fig. 2). However, Vero cells were unaffected by flower extract concentrations up to 700 g/ml and leaf extract concentrations up to 400 g/ml. The CC_{50} for the leaf and flower extracts of the C. azarolus was equal to 1203 and 870 µg/ml, respectively (Table 1).

The antiviral activity of each extract was expressed as a selectivity index (SI), which was calculated by dividing CC_{50} by IC_{50}. It was determined to be 9.50 and 10.41 for these flower and leaf extracts, respectively (Table 1). We also observed that the antiviral activities of leaf, flower extracts, and Acyclovir boosts with increasing concentrations (Fig. 3).

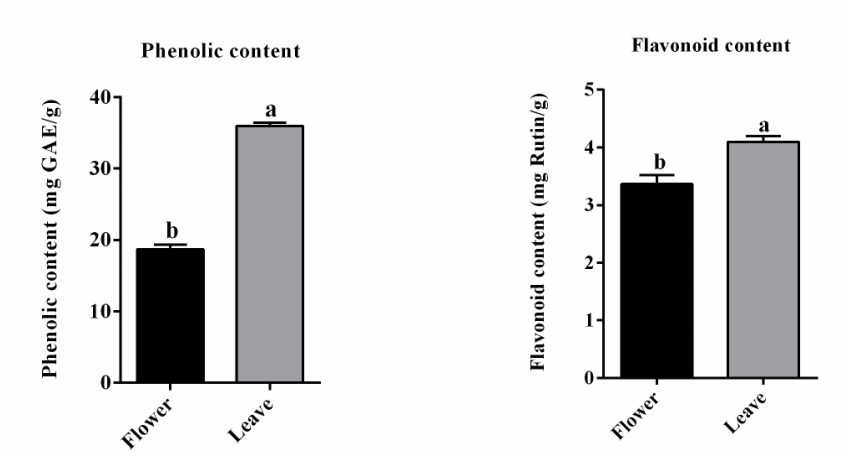

Figure 1. Phenolic and flavonoid content of Crataegus azarolus extracts. Each value represents the mean ± standard deviation. Columns with the same letter do not differ significantly at the 0.05 level (a, b, c, d, e, f).

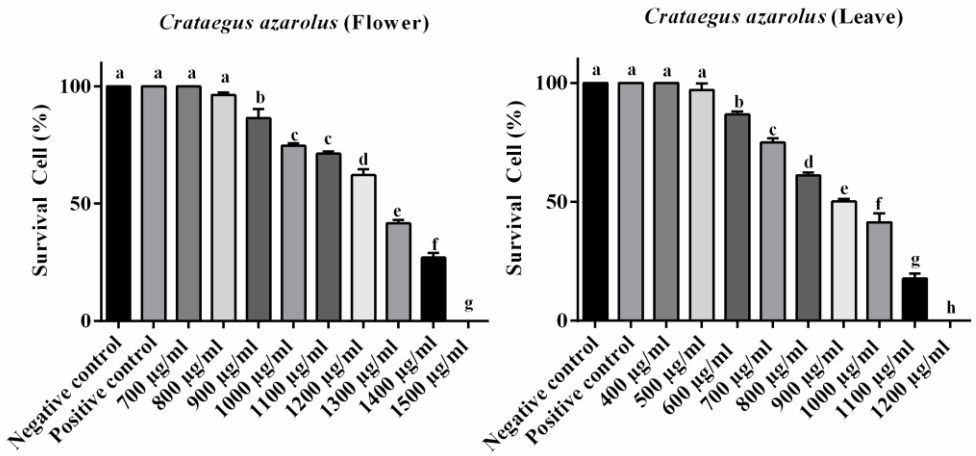

Figure 2. Survival cell at different concentrations of *Crataegus azarolus* extracts. Each value represents the mean ± standard deviation. Columns with the same letter do not differ significantly at the 0.05 level (a, b, c, d, e, f).

Table 1. Assessment of CC50, IC50, and selectivity index in the flower and leaf extracts of *C. azarolus*.

Extract	CC50	R2 (%)	IC50	R2 (%)	CC50/IC50 (SI)
Flower	1203.13	93.89	126.60	98.36	9.5033
Leaf	870.09	97.26	83.55	98.49	10.414

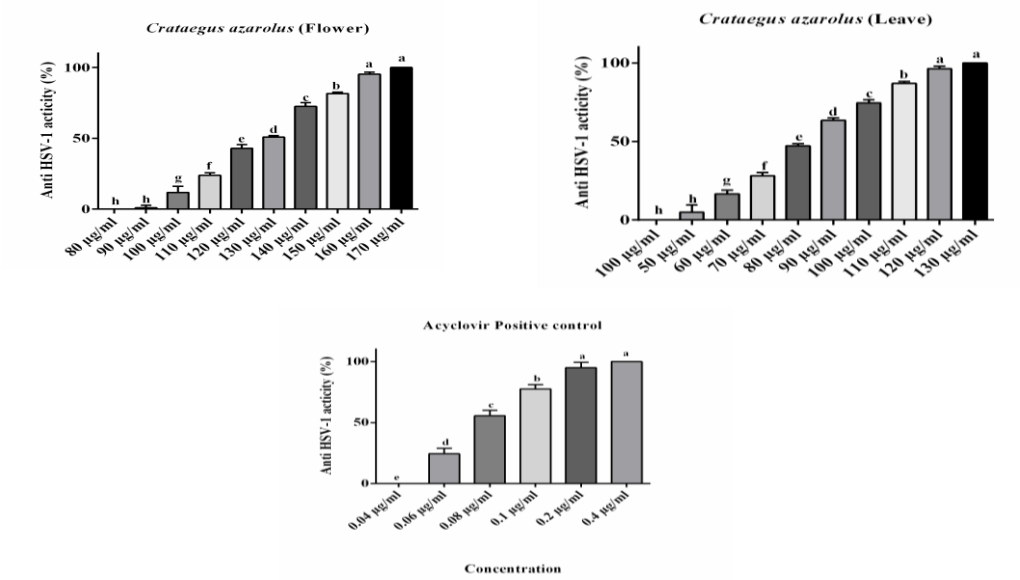

Figure 3. Anti-Herpes simplex virus-1 activity of different concentrations of Crataegus azarolus extracts and Acyclovir. Each value represents the mean ± standard deviation. Columns with the same letter do not differ significantly at the 0.05 level (a, b, c, d, e, f).

Discussion

Today, increasing concerns regarding the adverse effects and drug resistance associated with synthetic medications have led to growing interest in medicinal plants and natural compounds as alternative therapeutic agents for the prevention and treatment of various diseases (Hosseinzadeh et al. 2015; Gill et al. 2010; Dhama et al. 2018). In recent years, extensive investigations have focused on identifying plant-derived bioactive compounds with antimicrobial, antioxidant, anti-inflammatory, and antiviral properties. Among these medicinal plants, Crataegus azarolus (hawthorn) has attracted considerable attention because of its rich phytochemical composition and broad spectrum of biological activities. In the present study, we aimed to evaluate the antiviral potential of hawthorn extracts against herpes simplex virus. Our findings demonstrated that hawthorn leaves contain higher amounts of phenolic and flavonoid compounds compared with flowers. These results are consistent with previous investigations. Belkhir et al. (2013) reported that the total phenolic content in the leaves of C. azarolus was significantly higher than that observed in the peel and pulp of the fruit. Likewise, Moradi et al. (2018) reported total phenolic and flavonoid contents of 214.2 mg GAE/g and 28.6 mg RUT/g, respectively, in hawthorn leaf extracts. In another study, Yahyaoui et al. (2019) showed that the total phenolic and flavonoid contents in hawthorn pulp extracts collected from different geographical regions ranged from 8.52 to 69.46 mg GAE g−1 and from 1.52 to 8.78 mg QE g−1, respectively. The variations observed among different studies may be attributed to several factors, including differences in the plant part used, environmental conditions such as climate and geographical location, harvesting season, and extraction methods. These factors are known to influence the biosynthesis and accumulation of secondary metabolites in medicinal plants (Ansari et al. 2025; Nyakudya et al. 2020).

The results of the current study showed that the selectivity index of C. azarolus flower and leaf extracts was 9.5 and 10.41, respectively, indicating a favorable balance between antiviral efficacy and cytotoxicity. Similar findings were reported by Moradi et al. (2018), who observed a selectivity index of 9.97 for hawthorn leaf extract against herpes simplex virus. Furthermore, Belkhir et al. (2013) demonstrated that the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of C. azarolus peel and leaf extracts ranged from 59.35 to 118.71 mg/ml and 42.32 to 63.49 mg/ml, respectively. These findings further support the antimicrobial potential of this plant. Polyphenolic compounds are considered one of the most important contributors to the therapeutic properties of medicinal plants. Numerous studies have demonstrated that phenolic and flavonoid compounds possess strong antioxidant, antibacterial, antifungal, and antiviral activities (Orhan et al. 2007; Liu et al. 2012; Choi et al. 2014; Karimi et al. 2017). These compounds may interfere with viral adsorption, penetration, replication,

and assembly, thereby limiting viral propagation. In addition, polyphenols are capable of modulating host immune responses and reducing oxidative stress induced by viral infections. Several reports have shown that extracts obtained from different parts of C. azarolus exert inhibitory effects against both Gram-positive and Gram-negative bacteria, particularly Staphylococcus aureus and Streptococcus faecalis (Belkhir et al. 2013; Rjeibi et al. 2020; Nadia et al. 2014). Moreover, recent evidence suggests that C. azarolus extracts exhibit antiparasitic activity against Giardia lamblia (Abdulwahhab 2021), highlighting the broad-spectrum antimicrobial properties of this medicinal plant. Besides antimicrobial activity, C. azarolus possesses remarkable antioxidant capacity (Lakache et al. 2016). Oxidative stress is recognized as an important factor contributing to the pathogenesis of numerous infectious and inflammatory diseases. Therefore, the antioxidant activity of hawthorn may provide additional protection by neutralizing reactive oxygen species and preventing cellular damage. Furthermore, hawthorn leaves have been recognized as anti-inflammatory agents because of their ability to suppress pro-inflammatory mediators while promoting the secretion of anti-inflammatory cytokines (Kmail et al. 2017). Such immunomodulatory effects may contribute to controlling tissue injury associated with viral infections.

Interestingly, several plant-derived polyphenols have been shown to interact with the human microbiome, promoting the growth of beneficial bacteria and improving microbial diversity. Therefore, the biological effects of hawthorn may not be limited to direct antiviral activity but may also involve modulation of the microbiome and enhancement of host immune defenses (Gavanji et al. 2026; Liu et al. 2025; Edwards et al. 2017). The ability of C. azarolus leaf extract to inhibit herpes simplex virus replication has previously been demonstrated, mainly through interference with post-adsorption stages of viral proliferation (Moradi et al. 2018). The findings of the present study are in agreement with these observations and further confirm the potential of hawthorn as a valuable natural source of antiviral compounds.

CONCLUSIONS

The present study demonstrated that the methanolic extracts of Crataegus azarolus, particularly the leaf extract, possess significant antiviral activity against herpes simplex virus type 1 (HSV-1). The observed antiviral effects, together with the favorable selectivity index and the high content of phenolic and flavonoid compounds, suggest that this medicinal plant represents a valuable source of natural bioactive substances with therapeutic potential. In addition to its antiviral properties, the well-documented antioxidant, anti-inflammatory, and antimicrobial activities of C. azarolus may provide complementary benefits in controlling viral infections and reducing infection-associated tissue damage. Considering the increasing concerns regarding adverse effects and the emergence of resistance associated with conventional antiviral drugs, C. azarolus may serve as a promising natural alternative or adjunctive therapeutic agent. Nevertheless, further investigations are required to identify the specific active compounds responsible for its antiviral activity and to clarify their mechanisms of action. Moreover, in vivo studies and clinical trials are necessary to confirm the efficacy, safety, and potential therapeutic applications of C. azarolus in the management of herpes simplex virus infections. Overall, the findings of this study support the potential use of C. azarolus as a candidate for the development of novel plant-based antiviral formulations with fewer side effects than conventional chemical drugs.

Competing Interests: The authors declare that there are no competing interests.

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