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Phytochemical Landscape of *Solenostemma arghel (Delile) Hayne*: A Review on Phenolic Profiling, Extraction Optimization, and Structure-Activity Relationships

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Systematic Review

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Abstract

Solenostemma arghel is a desert medicinal plant traditionally used for metabolic and inflammatory disorders, yet comprehensive chemical and structure–activity relationship (SAR) evaluations remain limited. This review systematically analyzes 54 studies on its phytochemical composition and antioxidant bioactivity, emphasizing phenolic constituents. Findings identify hydroethanolic systems as optimal for phenolic recovery. Key bioactive compounds, including quercetin, kaempferol, rutin, and chlorogenic acid, demonstrate potent radical scavenging and oxidative stress modulation. SAR analysis suggests that hydroxylation patterns and glycosylation significantly dictate antioxidant potency. Comparative chemotaxonomic observations show that *S. arghel* maintains conserved biosynthetic features with related taxa while exhibiting distinct metabolite profiles. This review establishes the pharmacological relevance of *S. arghel* as a robust source of antioxidant phytochemicals. It further identifies critical research gaps, highlighting the necessity for advanced metabolomic profiling, standardized protocols, and integrated biological validation to facilitate translational medicinal applications.

1. Introduction

Natural products serve as a cornerstone for drug discovery, offering a vast chemical scaffold for therapeutic innovation. Among the diverse classes of secondary metabolites, phenolic compounds and flavonoids have gained prominence due to their multifaceted biological roles, primarily their antioxidant, anti-inflammatory, and cytoprotective effects [1, 2]. These properties are essential in mitigating oxidative stress-related pathologies, including diabetes, cardiovascular diseases, and cancer]1[.

Solenostemma arghel, commonly known as *Argel*, is a desert perennial shrub belonging to the Asclepiadoideae subfamily[3]. Historically, *Argel* has been an integral part of ethnomedicine in North, East Africa and parts of the Arabian Peninsula, particularly in Sudan, Egypt, Saudi Arabia, Palestine, Algeria[4], and Yemen[5]. Traditional practitioners utilize its leaves and stems to treat a broad spectrum of ailments, including gastrointestinal disorders (colic and spasms), respiratory issues (bronchitis and cough), and inflammatory conditions like rheumatism and sciatica [3, 6, 7]. In Sudan, it is specifically valued for treating jaundice, measles, and as a postpartum recovery remedy [3, 8].

Beyond its traditional reputation, modern pharmacological screening has revealed that *S. arghel* possesses significant biological activities that extend beyond its well-documented antioxidant capacity[3]. Recent studies have demonstrated its potent anti-cancer effects against acute myeloid leukemia (AML) and colon cancer cell lines [7, 9], as well as its hepatoprotective ability to normalize liver enzymes (AST and ALT) and reduce lipid peroxidation [10, 11] [Ref 5, 57]. Furthermore, its extracts have shown remarkable wound-healing efficiency and antimicrobial activity against pathogens like Staphylococcus aureus [10, 12].

Despite its profound ethno-pharmacological importance and the identification of unique metabolites such as pregnane glycosides (e.g., Argelosides) [3], the chemical literature on *S. arghel* remains

fragmented. There is a critical need to bridge traditional uses with modern analytical evidence, specifically concerning extraction efficiency and the structure-activity relationship (SAR) of its phenolic constituents.

This review provides a comprehensive and systematic evaluation of *S. arghel*, integrating 54 studies to clarify its phytochemical profile. It focuses on the impact of various extraction methodologies, advanced analytical platforms (UPLC/HRMS, NMR), and provides a comparative chemotaxonomic analysis with related Asclepiadaceae species. By consolidating these findings, the review aims to establish a rigorous chemical foundation for the safe and effective pharmaceutical application of *S. arghel*.

2. Methodology

To ensure a rigorous and transparent evaluation of *Solenostemma arghel*, this review followed the PRISMA 2020 guidelines. The primary objective is to synthesize evidence regarding the Total Phenolic Content (TPC) and Antioxidant Capacity, while correlating these findings with extraction efficiency and molecular structure.

2.1. Search Strategy and Data Sources

A systematic search was conducted across Google Scholar, PubMed, ScienceDirect, and Scopus, focusing on literature published between 2000 and 2025. This period was selected to capture high-resolution data obtained via modern analytical instrumentation, which is essential for accurate phenolic profiling.

The search utilized specific keywords: *Solenostemma arghel*, phenolic compounds, flavonoids, "antioxidant activity, DPPH scavenging, standardized extraction, and Asclepiadaceae Family.

The overall identification, screening, and eligibility workflow followed PRISMA guidelines and is illustrated in Fig. 1.

2.2. Inclusion and Exclusion Criteria

To maintain a high level of chemical accuracy, studies were screened based on the following strict criteria:

1. Chemical Focus: Studies must report quantitative data on phenolics, flavonoids, or specific antioxidant metabolites (e.g., Kaempferol derivatives).
2. Analytical Precision: Preference was given to research employing advanced techniques such as HPLC, UPLC/HRMS, or NMR for compound identification.

3. Standardized Assays: Inclusion of studies using validated antioxidant models (e.g., DPPH, FRAP, ABTS) or in *vivo* oxidative stress markers (e.g., SOD, MDA).
4. Extraction Parameters: Research that details the influence of solvent polarity (e.g., Ethanol, Methanol, Water) on the recovery of bioactive constituents.
5. Comparative Taxonomy: Studies providing chemical comparisons with other Asclepiadoideae species to define the unique antioxidant fingerprint of *S. arghel*.

Exclusion Criteria

Studies were excluded if they lacked quantitative chemical data, focused exclusively on non-chemical applications (e.g., insecticidal or agricultural), or utilized imprecise botanical identification. Out of 84 screened records, 54 studies met these rigorous standards.

2.3. Data Synthesis and Objectives

The extracted data were synthesized to address three core chemical questions:

- How do extraction variables influence the final TPC and antioxidant potency?
- What are the specific Structure-Activity Relationships (SAR) that drive the plant's radical scavenging ability?
- How does the antioxidant profile of *S. arghel* compare to its botanical relatives?

3. Phenolic Profile of Solenostemma arghel

3.1 Overview of Identified Phenolic Compounds

Phytochemical investigations have demonstrated that *Solenostemma arghel* possesses a chemically diverse phenolic profile comprising phenolic acids, flavonoids, and phenolic glycosides. These metabolites are central to the plant’s antioxidant [13,14], anti-inflammatory, and cytoprotective properties [3].

Chromatographic analyses—particularly HPLC and UPLC–MS—consistently highlight phenolic acids as one of the dominant classes. E-vanillic acid, pyrocatechol, pyrogallol, ferulic acid, and chlorogenic acid are frequently reported at relatively high levels [3,15]. Owing to their ability to donate hydrogen atoms or electrons, these compounds play key roles in neutralizing reactive oxygen species, thereby contributing to the plant’s antioxidant potential [16]. Flavonoids identified in *S. arghel* include naringenin, Hesperidin [3], quercetin, [17,18], kaempferol,and their glycosides such as kaempferol-3-*O*-glucoside (astragalin) and quercetin3-*O*-rhamnosyl-(1→2)-glucoside [19,20,21]. Their multiple hydroxyl groups and conjugated π-systems provide strong radical-scavenging capacities and metal-chelating properties, supporting their well-documented biological [2].

Notably, several novel phenolic glycosides—Solargins I–IV—have been isolated from the aerial parts of the plant. NMR and HR-ESI-MS analyses confirmed their structures as acylated phenolic glycosides with unique substitution patterns not previously reported in related taxa [22]. The discovery of these compounds underscores the distinct chemical signature of *S. arghel* within the Asclepiadaceae family and highlights its potential as a source of structurally unique antioxidant agents.

Table 1. Classification of phenolic constituents and representative bioactive compounds identified in *Solenostemma arghel* based on reported phytochemical profiling studies..

Phenolic class	Representative compounds	Notes	References
Phenolic acids	Vanillic acid, E-vanillic acid, Ferulic acid, Chlorogenic acid, Gallic acid, Pyrogallol, Caffeic acid	Highest concentration reported for Evanillic acid; abundant across leaves and aerial parts	[3, 23]
Flavonoids	Quercetin, Hesperidin, Narengin, Rutin, Kaempferol, Kaempferol glycosides (3-*O*-glucoside, 3*O*-arabinoside, 7-*O*rhamnoside), Apigenin	Major contributors to antioxidant activity; present in both free and glycosylated forms	[3,17,18,19,20,21]
Phenolic glycosides	Solargins I-IV	Newly identified; structurally unique glycosides	[3,15,22]
Other related metabolites	Rosmarinic acid, Coumarins, Cinnamic derivatives	Occur at moderate levels; contribute to total antioxidant capacity	[24]

Full quantitative list (µg/g) is provided in Supplementary Table S1.

The chemical structures of representative phenolic compounds identified in *Solenostemma arghel*, including Solargin I, E-vanillic acid, and rosmarinic acid, are presented in Figure 2 to illustrate structural diversity and support the phytochemical interpretation.

In summary, *S. arghel* contains a broad spectrum of phenolic metabolites ranging from low molecular-weight acids to highly glycosylated flavonoids. This diversity likely contributes to the plant's multifaceted antioxidant, anti-inflammatory, and cytoprotective effects.

3.2 Distribution Across Plant Parts

The qualitative and quantitative distribution of phenolic compounds in *Solenostemma arghel* varies notably among leaves, aerial parts, roots, and fruit peels, reflecting organ-specific physiological roles and metabolic specialization[4].

3.2.1. Leaves.

Leaves consistently show the highest phenolic concentrations, enriched particularly in Evanillic acid, pyrogallol, ellagic acid, hesperidin, and quercetin derivatives [24]. Reported total phenolic contents (TPC) typically range between 60–80 mg GAE/g DW, depending on solvent polarity and extraction technique [17,21,25,26]. The abundance of polyhydroxylated phenolics is consistent with the protective function of leaves against ultraviolet radiation and oxidative stress, explaining the strong antioxidant activity observed in ethanolic and methanolic extracts [2].

3.2.2. Aerial Parts

Extracts derived from combined aerial tissues (leaves, stems, and flowers) generally show slightly lower phenolic concentrations but greater structural diversity. These extracts commonly contain phenolic acids, flavonoids, glycosides, and the distinctive Solargins I–IV [3,22]. The mixed tissue composition facilitates the co-accumulation of both glycosylated metabolites and aglycones, making aerial parts particularly useful for comprehensive profiling[1].

While studies have not been held exclusively on plant's roots.

Understanding these organ-specific patterns is essential for optimizing extraction strategies and selecting suitable plant parts for pharmacological, nutraceutical, or industrial applications.

4. Integrated Comparative Analysis

4.1 Extraction Methods

The extraction of bioactive secondary metabolites from *Solenostemma arghel*, particularly phenolic compounds, is highly dependent on solvent polarity, extraction technique, and temperature [27]. This review analyzed diverse methodologies ranging from traditional decoctions to advanced instrumental extractions.

4.1.1. Solvent Selection and Efficiency

The literature indicates that aqueous methanol[28] and ethanol (60%–80%) [19] are the most effective solvents for recovering the highest Total Phenolic Content (TPC) and achieving the strongest antioxidant

activity (DPPH) [23].

- Methanol (80%): Consistently yielded a high concentration of flavonol glycosides, such as Kaempferol and Isorhamnetin derivatives [3,29].
- Ethyl Acetate: Frequently used in liquid-liquid partitioning to concentrate secondary metabolites and reduce polar sugars that interfere with isolation [30].
- Water: While mimicking traditional use (tea/decoction), pure aqueous extraction often yields lower concentrations of complex phenolics compared to hydro-alcoholic mixtures [12,10,19,31,32].

4.1.2. Conventional vs. Modern Techniques

The integration of the studies revealed a wide spectrum of techniques:

- Maceration and Soaking: The most common traditional-mimicking method, typically requiring 24–72 hours at room temperature [8,15,19,31,33]. Quantitative data shows that methanolic maceration provides a yield of approximately 10% [25].
- Soxhlet Extraction: Preferred for exhaustive extraction of air-dried leaves, often conducted at temperatures around 60–80°C [7,20,21,35]. While efficient, it carries a risk of degrading thermolabile ccompound.
- Modern Methods: Recent studies have introduced Ultrasound-Assisted Extraction (UAE) and orbital shaking at low temperatures (4°C) to preserve the metabolic fingerprint of the plant[36].

4.1.3 Sequential Fractionation

To isolate specific metabolite classes, a standardized sequential fractionation approach is observed across the studies:

1. Non-polar phase (Petroleum Ether/Chloroform) [10,23,37, 38]: Removes waxes and chlorophyll.
2. Intermediate phase (Ethyl Acetate) [30]: Concentrates flavonoids and phenolic acids.
3. Polar phase (n-Butanol) [23]: Captures complex glycosides (e.g., Argelosides and Stemmosides).

Table 2. Comparative overview of extraction techniques, solvent systems, and literature reported yields for *Solenostemma arghel*.

Extraction Technique	Solvent System	Reported Yield (%)	Key Findings & Observations	References
Maceration	80% MeOH/EtOH	10% – 27.1%	High yields achieved with longer durations (48-72h)	[5, 25,34]
Soxhlet	70-80% EtOH	~12.6g from 800g	Exhaustive; effective for large-scale glycoside recovery	[20,21,35]
Decoction (Hot Water)	Distilled Water	Varies	Mimics traditional use; optimized at 80°C for 20-90 min	[6,10, 12,17,39]
UAE & Cold Shaking	MTBE:MeOH (3:1)	High Selectivity	Highly effective for preserving thermolabile metabolites; involves liquidliquid partitioning.	[9,36,40]

4.2. Total Phenolic Content (TPC) and Antioxidant Capacity

The biological efficacy of *Solenostemma arghel* is intrinsically linked to its phenolic and flavonoid abundance [28]. This review synthesized quantitative data from studies, revealing a significant correlation between solvent choice, phenolic recovery, and subsequent antioxidant potency.

4.2.1. Comparative Analysis of TPC and TFC

Recent data indicates that the Ethanolic extract consistently outperforms other preparation methods in phenolic recovery[19,34]. For instance, TPC values in ethanolic extracts reached approximately 21.00 ± 0.65 mg GAE/g, compared to significantly lower yields in hot water extractions (8.76 ± 0.27 mg GAE/g) [9].

Flavonoid Concentration: A similar trend was observed in Total Flavonoid Content (TFC), where the ethanolic and methylene chloride:methanol (1:1) extracts showed superior concentrations (1.80 and 1.65 mg QE/g, respectively) compared to aqueous methods [9].

Thermal Sensitivity: The marked decrease in TPC in hot water extracts [9] suggests that certain phenolic constituents in *S. arghel* may undergo thermal degradation or poor solubility in hightemperature pure aqueous systems.

4.2.2. Antioxidant Mechanisms and Radical Scavenging

The antioxidant capacity of *S. arghel* was evaluated across various assays, showing a dosedependent response:

DPPH Radical Scavenging: The methanolic extract exhibited the highest inhibition percentage (86.12%) [28], demonstrating its potency as a primary antioxidant.

In *Vivo* Antioxidant Support: Beyond in *vitro* assays, studies on Wistar rats confirmed that *S. arghel* administration significantly enhances endogenous antioxidant enzymes [24,41,42].For example, a marked increase in Superoxide Dismutase (SOD) activity and a significant reduction in Malondialdehyde (MDA) (a lipid peroxidation marker) were recorded, particularly at a 7.5% dosage [24].

Selective Toxicity: An interesting finding in recent literature is the “Selective AntioxidantProoxidant” behavior, where extracts protect normal liver cells (reducing AST/ALT levels) while simultaneously inducing oxidative stress-mediated apoptosis in cancer cell lines [9].

Table 3. Relationship between extraction solvent polarity, phenolic content, and antioxidant activity of *Solenostemma arghel* extracts.

Extract Type	TPC (mg GAE/g)	TFC (mg QE/g)	DPPH Inhibition (%)	IC_{50} (mg/mL)	References
Ethanolic (80%)	21.00 ± 0.65	1.80 ± 0.06	59.60 ± 1.85	0.43 ± 0.01	[9]
DCM:MeOH (1:1)	18.40 ± 0.57	1.65 ± 0.05	55.00 ± 1.71	0.47 ± 0.01	[9]
Cold Water	17.90 ± 0.55	1.30 ± 0.04	35.50 ± 1.10	0.61 ± 0.02	[9]
Hot Water	8.76 ± 0.27	0.89 ± 0.03	33.30 ± 1.03	0.67 ± 0.02	[9]

TPC: Total Phenolic Content expressed as gallic acid equivalents (GAE).

TFC: Total Flavonoid Content expressed as quercetin equivalents (QE).

IC_{50}: Concentration required to inhibit 50% of DPPH radicals.

4.3. Structure-Activity Relationship (SAR) Analysis

The antioxidant and biological activity of *Solenostemma arghel* metabolites is strongly governed by their molecular architecture and substitution patterns [10,17,29,41]. Several consistent structure–activity relationship (SAR) trends were identified.

Flavonoids and Phenolic Hydroxylation:

Kaempferol, representing the flavonol subclass, exhibits strong radical scavenging capacity primarily due to the presence of free hydroxyl groups at positions C-3, C-5, and C-7 [23]. These hydroxyl groups enhance hydrogen atom donation and facilitate electron delocalization across the flavonoid backbone, stabilizing reactive oxygen species through resonance-supported radical intermediates.

Impact of Glycosylation:

Comparative analysis of kaempferol glycosides, particularly kaempferol-3-Oglucopyranoside, demonstrates a marked reduction in antioxidant potency relative to the aglycone form [23]. Glycosylation introduces steric hindrance and masks phenolic hydroxyl groups, thereby reducing hydrogen donation efficiency and limiting interaction with radical species or enzyme targets.

Pregnane Glycosides and Lipophilicity:

Argelosides and stemmosides, characterized by a pregnane steroidal backbone, display enhanced lipophilicity due to ester substitutions such as benzoyl or nicotinoyl groups [23]. Although these metabolites typically exhibit lower direct radical scavenging activity, their increased membrane permeability may enhance intracellular signaling and pharmacological bioavailability.

Synergistic Phytochemical Interactions:

The antioxidant profile of S. Arghel extracts arises from cooperative interactions between flavonoids and low-molecular-weight phenolic acids, including p-hydroxybenzoic acid [23]. These smaller phenolics may provide rapid radical neutralization, while flavonoids contribute sustained redox stabilization.

As illustrated in Figure 3, substitution of the C-3 hydroxyl group by glycosylation reduces antioxidant efficiency by limiting hydrogen donation and increasing steric hindrance.

4.4. Comparative Study within the Asclepiadaceae Family

To contextualize the phytochemical potency of *Solenostemma arghel*, a comparative analysis was performed against three representative species of the same family: *Calotropis PROCERA* [43,44], *Pergularia tomentosa* [45,46,47], and *Leptadenia pyrotechnica* [48,49,50]. The results highlight that *S. arghel* occupies a unique position in terms of phenolic abundance and antioxidant efficiency.

4.4.1. Phenolic and Flavonoid Yields

- *S. arghel* vs. *P. tomentosa*: While *Pergularia tomentosa* exhibited significant phenolic levels (reaching 32.46 mg GAE/g in methanolic extracts [46]), *S. arghel* showed a more robust profile in methanolic preparations (34.20 mg GAE/g[28]), While a higher diversity of flavonol glycosides were recorded in ethanolic extract [6].
- *Calotropis procera*: Research on *C. Procera* indicated moderate phenolic levels compared to *S. arghel*, with a primary focus on cardenolides rather than flavonoids [44], which explains its lower relative antioxidant activity in DPPH assays[43].

4.4.2. Antioxidant Potential (IC_{50} and Inhibition)

The radical scavenging capacity varies notably across the species:

- Efficiency: *S. arghel* demonstrated a very potent antioxidant profile with an IC_{50} of 0.14 mg/mL (Methanolic extract)[18]. This is comparable to the high potency found in *P. tomentosa* (IC_{50} = 0.34 mg/mL) [46], suggesting that these two species are the primary antioxidant drivers within the family.
- Inhibition Levels: At a concentration of 100 µg/mL, *C. Procera* showed a moderate inhibition of 46.6% [44], whereas *S. arghel* (at its optimal concentration) consistently exceeded 86.12% inhibition [28], indicating a higher density of active hydrogendonating phenolics.

4.4.3 Solvent Influence Across Species

A common trend observed across all four species is the superiority of Methanol and Ethanol over pure aqueous extracts. In *P. tomentosa*, the methanolic extract outperformed the ethanolic one [46,47], which aligns with our findings in *S. arghel* where hydro-alcoholic solvents are essential to bridge the polarity gap for maximum metabolite recovery [9,28].

Table 4. Comparative analysis of total phenolic content (TPC), antioxidant potency (IC_{50}), and primary bioactive compounds of *S. arghel* versus related *Asclepiadaceae* species.

Species	Primary Solvent	TPC (mg GAE/g)	Antioxidant Potency (IC_{50})	Main Bioactive Class	References
S. arghel	Methanol (80%),	21.00 – 43.76	0.14 – 0.43 mg/mL	Kaempferol glycosides,	[6,15,18, 19,28]
	ethanol (6080%)			Pregnane in ethanolic extract	
P. tomentosa	Methanol	32.46	0.34 mg/mL	Phenolics, Alkaloids	[46]
C. procera	Hydro-alcoholic	Moderate	~46.6% Inhibition	Cardenolides, Flavonoids	[44]
L. pyrotechnica	Methanol	Lower	1.95 mg /mL	Flavonoids, Tannins	[48,49,50]

GAE: Gallic Acid Equivalent; TPC: Total Phenolic Content; IC_{50}: Half Maximal Inhibitory Concentration.

4.5. Analytical Platforms for Phytochemical Profiling

The structural elucidation and quantification of *Solenostemma arghel* metabolites have evolved from basic spectrophotometric assays [28,51] to advanced high-resolution mass spectrometry [3,36]. This transition has enabled a deeper understanding of the plant's complex metabolic fingerprint, particularly its phenolic and glycoside content.

4.5.1. Spectrophotometric Assessments (TPC & TFC)

Early and routine screenings primarily rely on UV-Vis Spectrophotometry. The total phenolic content (TPC) is consistently measured using the Folin-Ciocalteu reagent (at 725 nm [7]), while total flavonoid content (TFC) is quantified via the Aluminum Chloride (AlCl_3) method [7,8,9,10] (at 415 nm [7]). While these methods are non-specific, they remain the gold standard for rapid antioxidant-related correlations.

4.5.2. Advanced Mass Spectrometry (UPLC/HRMS and LC-MS/MS)

The most significant leap in *S. arghel* research is the application of Ultra-Performance Liquid Chromatography coupled with High-Resolution Mass Spectrometry (UPLC/HRMS) [3,36].

- Precision Identification: The use of Orbitrap-type HRMS with Heated Electrospray Ionization (HESI), as reported in recent studies [36], has allowed for the identification of both polar and non-polar metabolites with exceptional mass accuracy.
- Metabolic Mapping: These platforms have been instrumental in identifying complex flavonoid glycosides (e.g., Kaempferol and Isorhamnetin derivatives) and the specific Argelosides series [36] and Solargin [3] in both positive and negative ionization modes.

4.5. 3. Nuclear Magnetic Resonance (NMR) Spectroscopy

For definitive structural confirmation of novel compounds, NMR (^{1}H and ^{13}C) remains indispensable [26,52]. Studies utilizing high-field spectrometers (e.g., Bruker Avance 500 MHz [23,30]) have successfully elucidated the substitution patterns of various pregnane glycosides, such as Solargin I and Stemmosides, as well as rare phenolic glycosides [23].

4.5.4. Gas Chromatography-Mass Spectrometry (GC-MS)

While *S. arghel* phenolics are generally non-volatile, GC-MS has been effectively utilized to analyze the silylated extracts or volatile components. It provides complementary data on lipophilic constituents and small phenolic acids [15,52], supported by extensive spectral libraries for metabolite identification.

Table 5. Summary of analytical platforms and methodologies employed for the phytochemical profiling and structural elucidation of *Solenostemma arghel* metabolites.

Technique	Application in *S. arghel*	Specific Advantages	Key Identified Metabolites	References
UPLCHRMS (Orbitrap)	Comprehensive metabolic profiling	Ultra-high sensitivity & mass accuracy; identification of minor traits	Kaempferol glycosides, Argelosides, Cardenolides	[36]
NMR (500 MHz)	Absolute structural elucidation	Definitive for novel scaffolds and stereochemistry	Solargins, Stemmosides , Pregnane derivatives	[23,30]
HPLC-DAD	Routine quantification	Reliable for TPC/TFC and major flavonoid peaks	Quercetin, Kaempferol, Phenolic acids	[3,26,51]
GC-MS	Analysis of volatile & lipophilic fractions	Rapid identification of small molecules and fatty acids	Phytol, Squalene, simple Phenolic acids	[3,18,20, 36,41,52]
UV–Vis	Global screening (TPC/TFC)	Highthroughput; costeffective for initial assays	Total Phenolics/Flavonoids	[15,18,28,42]

Table S1
Phenolic compounds identified in *Solenostemma arghel*

Category	Compound	Amount (µg/g)	Plant Part	Reference
Phenolic acids	Pyrocatechol	9519.95	Aerial parts	]3[
	Ferulic acid	3221.41	Aerial parts	[3]
	Chlorogenic acid	3221.41	Aerial parts	[3]
	Gallic acid	2730.85	Aerial parts	[3]
	Pyrogallol	4666.3	Leaves	]8[
	4-Amino benzoic acid	206.2	Leaves	[8]
	Catechol	1292.2	Leaves	[8]
	Epicatechin	749.8	Leaves	[8]
	Caffeine	372.5	Leaves	[8]
	p-Hydroxy benzoic acid	1940.7	Leaves	[8]
	Caffeic acid	623.8	Leaves	[8]
	Vanillic acid	938.8	Leaves	[8]
	Iso-ferulic acid	364	Leaves	[8]
	E-vanillic acid	26289.4	Leaves	[8]
	Resveratrol	115.2	Leaves	[8]
	Ellagic acid	3451.8	Leaves	[8]
	A- Coumaric acid	638.4	Leaves	[8]

4.6. Toxicological Profile and Safety Assessment

The safety of *Solenostemma arghel* is a subject of significant discussion in the literature, with results varying based on dosage, route of administration, and study duration. Most of the included studies support the biosafety of the plant at traditional and moderate therapeutic doses [5,17,24,25,39,40,53]. For instance, acute toxicity tests following OECD guidelines reported no mortality or clinical signs of toxicity at doses up to 2000 mg/kg [41]. Furthermore, some investigations highlighted a selective toxicity, where the extract induced apoptosis in cancer cells without affecting normal white blood cells [9].

However, significant toxicological effects and embryotoxicity were observed in specific experimental conditions, primarily in studies from Sudan [8,54]. Key findings from these studies include:

Embryotoxicity: Intraperitoneal injection of 500 mg/kg during the organogenesis period (days 7–16 of pregnancy) led to external malformations in 25% of fetuses, including missed limbs, resorption, and cytoplasmic vacuolation in fetal liver tissues [8].

Organ Toxicity: High-dose administration (2000 mg/kg to 500 mg/kg) was associated with elevated liver enzymes (AST, ALT, and ALP) and histopathological changes such as necrosis and congestion in the liver and kidneys [8,52].

Hematological Impacts: Prolonged exposure at certain concentrations resulted in macrocytic hypochromic anemia, evidenced by increased MCV and decreased MCHC [11].

Methodological Analysis of Discrepancies:

The apparent contradiction between traditional safety and these experimental findings can be attributed to methodological factors:

Route of Administration: The use of intraperitoneal (IP) injection [8,52] bypasses the gastrointestinal barriers, delivering alkaloids and glycosides directly into the bloodstream, which increases toxicity compared to oral consumption.

Dosage: The doses reaching 5 g/kg [8] far exceed typical human traditional use.

In conclusion, while *S. arghel* demonstrates a wide safety margin at traditional doses [17], its concentrated use during pregnancy or at exceptionally high doses may pose risks of organ damage and embryotoxicity[8].

5. Discussion

The comprehensive analysis of *Solenostemma arghel* secondary metabolites highlights a clear transition from traditional decoctions to standardized, high-potency extracts. The superiority of 80% Ethanol in recovering the highest TPC (21.00 ± 0.65 mg GAE/g) over aqueous methods is a critical finding. Chemically, this is attributed to the balanced polarity of hydro-alcoholic mixtures, which facilitates the solubilization of both simple phenolic acids and complex flavonoid glycosides like Kaempferol.

A pivotal point in this review is the Structure-Activity Relationship (SAR). Our synthesis confirms that while *S. arghel* is rich in glycosylated flavonoids, its peak antioxidant performance is driven by the aglycone forms (e.g., Kaempferol). The steric hindrance caused by sugar moieties in glycosides explains the lower values in certain extracts. Furthermore, the presence of cardenolides and pregnanes, although not the primary antioxidants, contributes to the plant's selective cytotoxicity and hepatoprotective effects, suggesting a synergistic multitarget pharmacological mechanism.

Compared to other Asclepiadaceae species, *S. arghel* demonstrates a unique chemical fingerprint that combines high phenolic density with a manageable safety profile. The observed toxicity in high-dose Sudanese studies (500 mg/kg) serves as a vital reminder that therapeutic efficacy is strictly dose-dependent, reinforcing the need for precise laboratory standardization.

6. Conclusion

This review successfully consolidated fragmented data on *Solenostemma arghel* , establishing a rigorous chemical baseline for its antioxidant and phenolic profile. The integration of 54 contemporary studies confirms that the plant's bioactivity is a direct consequence of its rich flavonol and pregnane content. We conclude that ethanol-based extraction and UPLC/HRMS analysis are the most reliable methods for isolating and identifying its potent metabolites. While *S. arghel* remains safe within traditional dosage ranges, its potential for embryotoxicity at extreme concentrations necessitates caution. Future research should focus on the clinical translation of these findings, particularly the development of standardized formulations for inflammatory and oxidative stress-related disorders.

Recommendations and Future Research Directions

Based on the current evidence synthesis, several priority research directions are recommended to advance the pharmacological and translational potential of *Solenostemma arghel*:

1. Advanced Metabolomic and Chemoinformatic Profiling

Future investigations should employ high-resolution metabolomic platforms, including LC– MS/MS and NMR-based metabolomics, to establish comprehensive chemical fingerprints of S. Argel. Integration with chemoinformatics and molecular docking approaches may facilitate the identification of bioactive lead compounds and predict target-specific interactions relevant to oxidative stress–related disorders.

2. Standardization of Extraction and Phytochemical Quantification

Considerable variability exists among reported extraction procedures and analytical methodologies. Standardized extraction protocols, solvent optimization, and validated quantitative analytical techniques are necessary to ensure reproducibility, inter-study comparability, and reliable correlation between phytochemical composition and biological activity.

3. Mechanistic Biological Validation

Although antioxidant activity has been widely reported, further mechanistic studies are required to elucidate intracellular signaling pathways, enzyme modulation, and molecular targets influenced by *S. arghel* phenolics. Multi-assay validation strategies combining in vitro cellular models with in *vivo* experimental systems are strongly recommended.

4. Toxicological and Safety Evaluation

Comprehensive toxicological assessments, including acute, sub-chronic, and chronic toxicity models, remain limited. Establishing safety profiles and therapeutic index parameters is essential to support the potential clinical and nutraceutical application of *S. arghel* extracts.

5. Structure–Activity and Bioavailability Studies

Further research should focus on clarifying the influence of phenolic structural modifications, including hydroxylation patterns and glycosylation, on biological activity and pharmacokinetic behavior. Studies addressing compound stability, metabolism, and bioavailability are necessary to strengthen drug development prospects.

6. Translational and Clinical-Oriented Research

Future work should expand toward formulation development, delivery system optimization, and preclinical validation of standardized extracts or isolated compounds. Such approaches may accelerate the translation of *S. arghel* phytochemicals into potential therapeutic or preventive applications.

Declarations

Conflicts of Interest

The author declare no conflict of interest.

Declarations of Generative AI in Scientific Writing

During the preparation of this work, the author used the AI tool Grammarly exclusively for the purpose of improving linguistic quality, correcting grammatical errors, and refining the phrasing style. The author confirms that the collection and synthesis of qualitative and quantitative data, the development of the Structure-Activity Relationship (SAR) analysis, and the formulation of scientific conclusions are the original and human effort of the author. The author bears full responsibility for the accuracy, integrity, and reliability of all information presented in this paper.

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References

1. Newman DJ, Cragg GM (2020) Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. ;83(3):770–803. Doi 1021/acs.jnatprod.9b01285
2. Ogbodo JO, Agbo CP, Echezona AC, Ezike TC, Emencheta SC, Onyia OC et al (2022) Therapeutic Role of Phenolic Antioxidants in Herbal Medicine. In: Ogbodo JO (ed) Therapeutic Roles of Phenolic Antioxidants in Herbal Medicine. University of Nigeria, Nigeria, pp 1–22
3. Abdel-Sattar E, El-Shiekh RA (2024) A Comprehensive Review on Solenostemma argel (Del.) Hayne, An Egyptian Medicinal Plant. Bull Fac Pharm Cairo Univ 62(1):3. 10.54634/2090-9101.1050
4. Teia FKF (2018) A review of Solennostemma argel: Phytochemical, pharmacological activities and agricultural applications. J Ayu Herb Med 4(2):99–101
5. Ibrahim EA, Gaafar AA, Salama ZA, El Baz FK (2015) Anti-inflammatory and Antioxidant Activity of Solenostemma argel extract. Int J Pharmacogn Phytochem Res 7(4):635–641
6. Shafek RE, Shafik NH, Michael HN (2012) Antibacterial and Antioxidant Activities of Two New Kaempferol Glycosides Isolated from Solenostemma argel Stem Extract. Asian J Plant Sci 11(3):143–147
7. Maad AH, AL-Gamli AH, Shamarekh KS, Refat M, Shayoub ME (2024) Antiproliferative and Apoptotic Effects of Solenostemma argel Leaf Extracts on Colon Cancer Cell Line HCT-116. Biomed Pharmacol J 17(3):1987–1996. 10.13005/bpj/3001
8. Mustafa NME, Osman NA, Satti S, Gameel AA, El-hadiyah TM Teratogenic Potential of Solenstemma Argel Extract in Wistar Albino Rats. Research Square [Preprint]. 2021 [cited 2026 Feb 7]. Available from: https://doi.org/10.21203/rs.3.rs-847368/v1
9. Nassr-Allah AA, Aboul-Enein AM, Aboul-Enein KM, Lightfoot DA, Cocchetto A, ElShemy HA (2009) Anti-cancer and anti-oxidant activity of some Egyptian medicinal plants. J Med Plants Res 3(10):799–808
10. Hamadnalla HMY, El-Jack MM (2019) Phytochemical Screening and Antibacterial Activity of Solenostemma argel: A Medicinal Plant. Acta Sci Agric 3(6):02–4
11. Iman AAM, Omar FI, Adam SIY (2019) Potential Hepato-healing effect of Solenostemma argel and Origanium majorana against Carbon Tetrachloride-induced Hepatic Damage in Rats. Neelain J Sci Technol 3(1):1–6
12. Ahmad MZ, Ahmad J, Abdel-Wahab BA, Alasiri AS, Alotaibi HF, Saeeds AM et al (2023) Green Synthesis of Silver Nanoparticles from Solenostemma argel Leaf Extract: Characterization and Wound Healing Activity. Sci Adv Mater 15(5):673–681
13. Dhshan AI, Goda MS, Ibrahim AK (2025) Solenostemma argel: A Comprehensive Review of its Photochemistry and Pharmacological Activities. Rec Pharm Biomed Sci 9(2):121–133
14. Ahmed RH, Mustafa DE, Mohamed YS (2019) Anti-diabetic plants used in Sudanese folk medicine and their phytochemical constituents: A review. J Adv Res Pharm Sci Pharmacol Interv 3(1):1–8
15. Abdel-Motaal FF, Maher ZM, Ibrahim SF, El-Mleeh A, Behery M, Metwally AA (2022) Comparative Studies on the Antioxidant, Antifungal, and Wound Healing Activities of Solenostemma arghel Ethyl Acetate and Methanolic Extracts. Appl Sci. ;12(9):4121. Doi 3390/app12094121

16. Upaganlawar AB, Dhote VV, Raja MKM (eds) (2022) Health benefits of phenolic antioxidants. Nova Science, New York
17. Ahmed MM (2016) Hepatoprotective role of Solenostemma argel growing in Egypt on ethanol induced oxidative damage in rats. Turk J Biochem 41(6):445–452. 10.1515/tjb-20160211
18. El-Zayat MM, Eraqi MM, Alfaiz FA, Elshaer MM (2021) Antibacterial and antioxidant potential of some Egyptian medicinal plants used in traditional medicine. J King Saud Univ Sci 33(5):101466. 10.1016/j.jksus.2021.101466
19. Mohamed Ahmed IA, Al-Juhaimi F, Adisa AR, Adiamo OQ, Babiker EE, Osman MA et al (2020) Optimization of ultrasound-assisted extraction of phenolic compounds and antioxidant activity from Argel (Solenostemma argel Hayne) leaves using response surface methodology (RSM). J Food Sci Technol 57(8):3071–3080. 10.1007/s13197-020-04340-6
20. Alkuwayti MA (2023) Anti-Staphylococcus aureus Activity of the Aqueous Ethanolic Extract of Solenostemma argel Aerial Parts. J Pure Appl Microbiol. ;17(4):2581-90. Doi 22207/JPAM.17.4.55
21. Osman HM, Shayoub ME, Babiker EM (2013 May-Aug) The effect of Solenostemma argel on anemiarelated parameters in Albino Rats and Rabbits. Saudi J Health Sci 2(2):7–11
22. Kamel MS (2003) Acylated phenolic glycosides from Solenostemma argel. Phytochemistry 62(8):1247–1250
23. Demmak RG, Bordage S, Bensegueni A, Boutaghane N, Hennebelle T et al (2019) Chemical Constituents from Solenostemma argel and their Cholinesterase Inhibitory Activity. Nat Prod Sci 25(2):115–121. 10.20307/nps.2019.25.2.115
24. Azer DD, Kahlil AF, Hafez AA, El-Hadidy EM (2021) Hepato Effect of Argel Herb (Solenostemma argel) against Carbon Tetra Chloride Induced Liver damage in Albino Rats. Int J Fam Stud Food Sci Nutr Health 4(1):142–161
25. Elsanhoty RM, Soliman MSM, Khidr YA, Hassan GOO, Hassan ARA, Aladhadh M et al (2022) Pharmacological Activities and Characterization of Phenolic and Flavonoid Compounds in Solenostemma argel Extract. Molecules. ;27(23):8118. Doi 3390/molecules27238118
26. Ounaissia K, Pertuit D, Mitaine-Offer AC, Miyamoto T, Tanaka C, Delemasure S et al (2016) New pregnane and phenolic glycosides from Solenostemma argel. Fitoterapia 114:98–104. 10.1016/j.fitote.2016.08.002
27. Morrison RT, Boyd RN (1992) Organic Chemistry, 6th edn. Prentice Hall, Englewood Cliffs (NJ)
28. El-Beltagi HS, Abdel-Mobdy YE, Abdel-Rahim E (2017) Toxicological influences of cyfluthrin attenuated by Solenostemma argel extracts on carbohydrate metabolism of male albino rats. Fresen Environ Bull 26(2a):1673–1681
29. Hasim H, Faridah DN, Qomaliyah EN, Afandi FA (2023) Pancreatic Lipase Inhibition Activity in Lipid Absorption Using Traditional Plants: A Systematic Review and Meta-Analysis. Indones J Chem 23(2):568–582. 10.22146/ijc.76873
30. Hassabelrasoul H, Moriguchi M, Kang B, Siribel AA, Kuse M (2021) Isolation and identification of metabolites from ethyl acetate leaf extract of Solenostemma argel. Agric Nat Resour 55(5):757–

763. 10.34044/j.anres.2021.55.5.06

31. Al-Juhaimi FY, Shahzad SA, Ahmed AS, Adiamo OQ, Mohamed Ahmed IA, Alsawmahi ON et al (2018) Effect of Argel (Solenostemma argel) leaf extract on quality attributes of chicken meatballs during cold storage. J Food Sci Technol. ;55(5):1781-92. Doi 1007/s13197-018-3092-2
32. Abdelmuhsin AA, Ibrahim SM, Kehail MA, Sulieman AME (2024) Antibacterial, phytochemical and GC-MS analyses of argel (Solanum argel) leaves. Cell Mol Biol 70(9):106 10.14715/cmb/2024.70.9.15
33. Abouzaid OA, Mansour SZ, Sabbah F (2018) Evaluation of the antitumor activity of Solenostemma argel in the treatment of lung carcinoma induced in rats. Benha Vet Med J 35(1):178–189
34. Farah AA, Ahmed EH (2016) Beneficial antibacterial, antifungal and anti-insecticidal effects of ethanolic extract of Solenostemma argel leaves. Mediterr J Biosci 1(4):184–191
35. Osman HM, Shayoub ME, Ahmed ME, Babiker EM (2015) The effect of Solenostemma argel leaves extract on status of induced lipid constituents in albino rats. Int J Dev Res 5(3):3828–3830
36. El-Shiekh RA, Salem MA, Mouneir SM, Hassan A, Abdel-Sattar E (2021) A mechanistic study of Solenostemma argel as anti-rheumatic agent in relation to its metabolite profile using UPLC/HRMS. J Ethnopharmacol 265:113341. 10.1016/j.jep.2020.113341
37. Ahmed EM, Nour BY, Mohammed YG, Khalid HS (2010) Antiplasmodial activity of some medicinal plants used in Sudanese folk-medicine. Environ Health Insights 4:1–6
38. Innocenti G, Dall'Acqua S, Sosa S, Altinier G, Della Loggia R (2005) Topical anti-inflammatory activity of Solenostemma argel leaves. J Ethnopharmacol 102(3):307–310. 10.1016/j.jep.2005.06.007
39. Hanafi N, Mansour SZ (2010) Antitumor Efficacy of Salenostemma Argel and/or y-Irradiation Against Ehrlich Carcinoma. J Biol Sci 10(6):468–479
40. Taj Al-Deen A, Al-Naqeb G (2014) Hypoglycemic effect and in vitro antioxidant activity of methanolic extract from Argel (Solenostemma Argel) plant. Int J Herb Med 2(2):128–131
41. El-Shiekh RA, Salama A, Al-Mokaddem AK, Abdel-Sattar E (2021) Gastroprotective effect of mucilage fraction from Solenostemma argel via cytoprotection and attenuation of oxidative stress, inflammation and apoptosis. J Herbmed Pharmacol 10(2):232–240. 10.34172/jhp.2021.26
42. El-shiekh RA, Al-Mahdy DA, Mouneir SM, Hifnawy MS, Abdel-Sattar EA (2019) Anti-obesity effect of argel (Solenostemma argel) on obese rats fed a high fat diet. J Ethnopharmacol 238:111893. 10.1016/j.jep.2019.111893
43. Mehmood T, Arshad H, Nawaz S, Ullah A, Hafeez A, Anwar F et al (2020) Pharmaceutical potential and phenolics profiling of leaves and bark of Calotropis procera in relation to extraction solvents. Pharm Chem J 54(6):631–639. 10.1007/s11094-020-02250-
44. Dixit A, Sahani V, Khareya AK, Tiwari V. Antioxidant activity of hydroalcoholic extract of leaves of Calotropis procera. GSC Biol Pharm Sci. 2023;22(01):072 – 5. Doi: 30574/gscbps.2023.22.1.0011.
45. Hosseini Kahnouj SH, Ayyari M, Azarnivand H, Piacente S, Zare Chahouki MA. Pergularia tomentosa, from Traditional Uses to Ecology and Phytochemistry. J Med Plants. 2017;16(63):146 – 58.

46. El-Sawi NM, Olish M, Gad MH. Phytochemical analysis, chemical composition and antioxidant activity of different Pergularia tomentosa extracts. Sohag J Sci. 2025;10(1):47–53. Doi: 10.21608/sjsci.2024.320378.1222.
47. Yakubu R, Jibril FM, Lukman A, Sheikh F. Trends for Antioxidant Power of Phytochemicals from Pergularia tomentosa L. (Asclepiadacea) Whole Plant. Sch Acad J Pharm. 2015;4(2):74–80.
48. Alkaltham MS, Hayat K, Salamatullah AM, Ahmed MA, Hassan AB. Effect of Microwave and Conventional Heat Treatment on Total Phenolic Compounds, HPLC Phenolic Profile, and Antioxidant Activity of Leptadenia pyrotechnica (Forssk.) Decne Stem. Appl Sci. 2023;13(24):13222. Doi: 10.3390/app132413222.
49. Munazir M, Qureshi R, Munir M. Preliminary phytochemical screening of roots and aerial parts of Leptadenia pyrotechnica. Pak J Bot. 2015;47(2):659 – 64.
50. Mohamud SG, Ismaiel SM, Haroun SA, El-Sherbeny GA, Radwan AM. Comprehensive Phytochemical and GC-MS Analysis of Leptadenia pyrotechnica: Unveiling Antioxidant and Antibacterial Potential. Int J Theor Appl Res. 2025;4(1):589 – 99. Doi: 10.21608/LJTAR.2025.343309.1097.
51. Abd Alhady MR, Hegazi GA, Abo El-Fadl RE, Desoukey SY. Biosynthetical capacity of kaempferol from in vitro produced Argel (Solenostemma argel (Del.) Hayne) callus. Res J Appl Biotechnol. 2016; (Special volume):134 – 43.
52. Benmaarouf DK, China B, Pinto DCGA, Aliboudhar H, Boulahlib S, Zenia S, et al. In vivo Acute Toxicity, Analgesic Activity and Phytochemical Characterization of Solenostemma argel (Del) Hayne Essential Oil. J Appl Biotechnol Rep. 2023;10(2):976 – 83. Doi: 10.30491/JABR.2023.385652.1606.
53. Taha LE, Bakhit SMA, Al-Sa'aidi JAA, Uro ABO. The anti-hyperglycemic effect of Solenostemma argel compared with Glibenclamide. Al-Qadisiya J Vet Med Sci. 2014;13(2):113-7.
54. Mohammed SE, Azhari HE, Abd AM, Rasha MR, Mona AA. Determination of acute toxicity of Solenostemma argel and it is effect on the vital organs and heamatological parameters. Indo-Global Res J Pharm Sci. 2013;3(2):11 – 7.

Figures

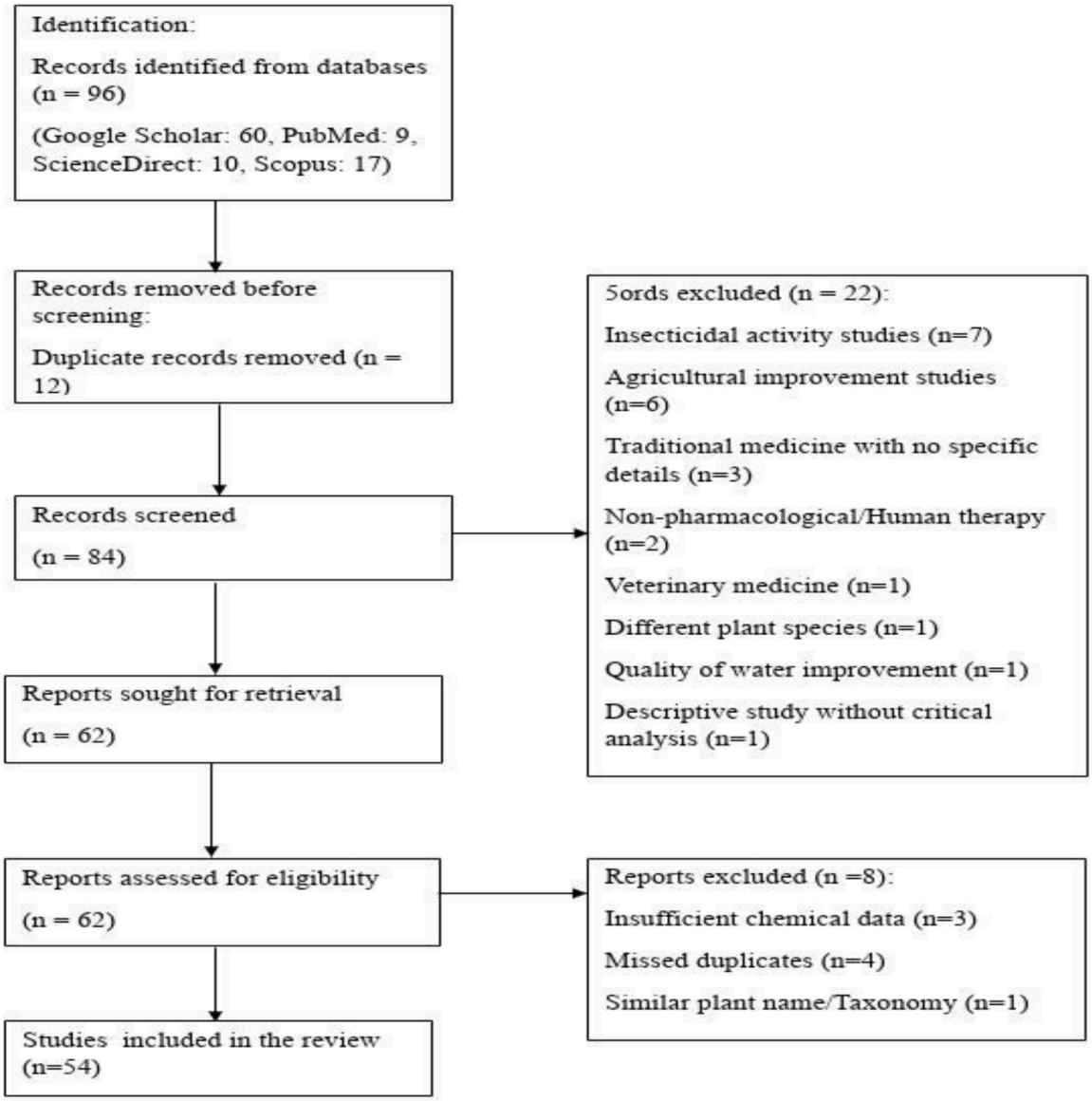


Figure 1

PRISMA 2020 flow diagram illustrating the identification, screening, eligibility, and final inclusion of studies evaluating the phenolic composition and antioxidant activity of *Solenostemma arghel*.

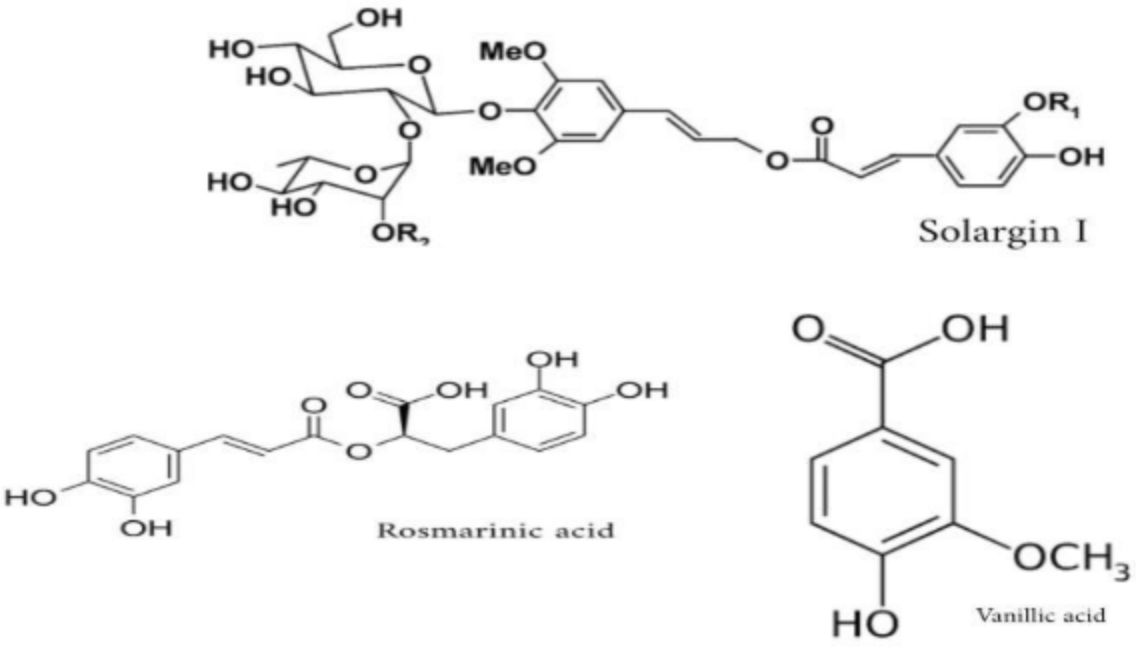


Figure 2

Chemical structures of representative phenolic compounds identified in *Solenostemma arghel*, including Solargin I, E-vanillic acid, and rosmarinic acid.

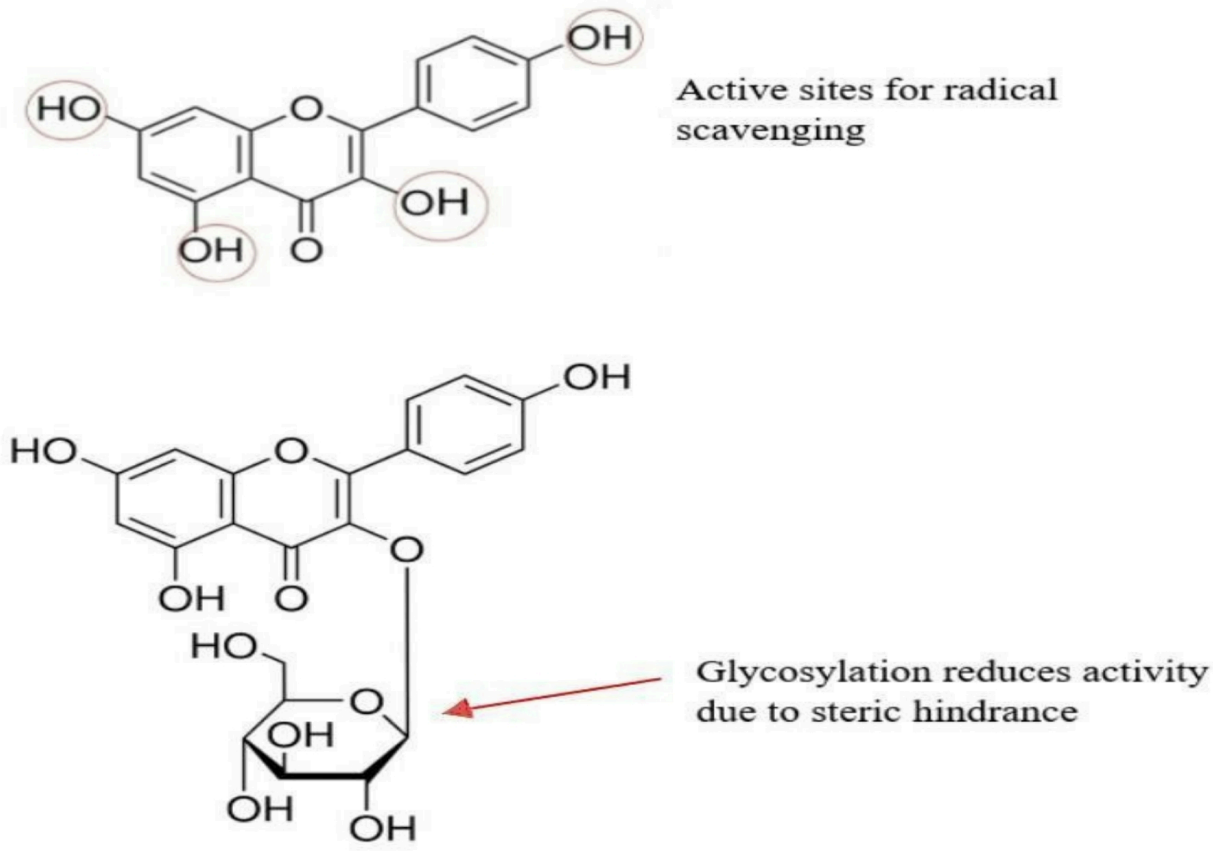


Figure 3

Structural comparison between kaempferol and kaempferol-3-O-glycoside highlighting key functional groups influencing antioxidant activity.