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Romanian Wild-Growing *Chelidonium majus*—An Emerging Approach to a Potential Antimicrobial Engineering Carrier System Based on AuNPs: In Vitro Investigation and Evaluation

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Abstract: Novel nanotechnology based on herbal products aspires to be a high-performing therapeutic platform. This study reports the development of an original engineering carrier system that jointly combines the pharmacological action of *Chelidonium majus* and AuNPs, with unique properties that ensure that the limitations imposed by low stability, toxicity, absorption, and targeted and prolonged release can be overcome. The metabolite profile of Romanian wild-grown *Chelidonium majus* contains a total of seventy-four phytochemicals belonging to eight secondary metabolite categories, including alkaloids, amino acids, phenolic acids, flavonoids, carotenoids, fatty acids, sterols, and miscellaneous others. In this study, various techniques (XRD, FTIR, SEM, DLS, and TG/DTG) were employed to investigate his new carrier system’s morpho-structural and thermal properties. In vitro assays were conducted to evaluate the antioxidant potential and release profile. The results indicate 99.9% and 94.4% dissolution at different pH values for the CG-AuNPs carrier system and 93.5% and 85.26% for greater celandine at pH 4 and pH 7, respectively. Additionally, three in vitro antioxidant assays indicated an increase in antioxidant potential (flavonoid content 3.8%; FRAP assay 24.6%; and DPPH 24.4%) of the CG-AuNPs carrier system compared to the herb sample. The collective results reflect the system’s promising perspective as a new efficient antimicrobial and anti-inflammatory candidate with versatile applications, ranging from target delivery systems, oral inflammation (periodontitis), and anti-age cosmetics to extending the shelf lives of products in the food industry.

Keywords: great celandine; AuNPs; carrier system; secondary metabolites; antioxidant activity; dissolution profile

1. Introduction

Chelidonium majus (Papaveraceae family) is the sole representative of the *Chelidonium* genus in the Romanian flora and, respectively, in that of Europe [1]. Its common names include greater celandine, swallow-wort, rostopască, negelarită in Romanian, and bai-qu-cai in Chinese. Greater celandine (GC) has been recognized as a plant with both medicinal and toxic properties since ancient times, with mentions dating back to ancient Europe and in Chinese traditional medicine [2]. From Dioscorides, Pliny the Elder, and Galenus until the XIV century, greater celandine was recommended for ocular ailments. In medieval Europe, the plant was used also for treating ulcers, cutaneous eczema, jaundice, and colic. Paracelsus mentioned the benefits of this plant for treating hepato-biliary conditions. Currently, greater celandine is appreciated in traditional European medicine, especially in the central and eastern regions, being recognized for its exceptional therapeutic properties, especially in dermatological conditions (e.g., eczema, verrucae, circumscribed cutaneous carcinomas), hepato-biliary (anti-jaundice) conditions, chole cytopathies, biliary lithiasis, gastrointestinal spasms, eye infections, and inflammation [3–6]. Modern research has reported the presence of a large variety of biomolecules (alkaloids, flavonoids, carotenoids, lectins, phenolic acids, volatile oils, and others) and, thus, remarkable biological activity (antibacterial, antimicrobial, antifungal, antiviral, anti-inflammatory, antitumoral, anti-spasmodic, hepato-protective, analgesic, and immunomodulatory) [7–15].

Cutting-edge nanotechnology-based phytochemical carriers have emerged as promising candidates with highly improved in vivo activity due to the overcoming of the drawbacks (low bioavailability, chemical, and thermal stability, and selectivity) of conventional herbal formulations [16]. Engineering phytochemical carriers are the most successful approaches, with highly improved in vivo activity. These carriers effectively overcome all the challenges posed by conventional herbal formulations, including low bioavailability, selectivity, and chemical and thermal stability [17].

Of all the metallic nanoparticles, gold nanoparticles are particularly well-suited for various biomedical applications thanks to their unique properties, such as versatile tailored surfaces, excellent stability, easy cellular uptake, and minimal toxicity. As a result, current research addresses the design of novel drug delivery systems that can mitigate drug resistance in cancer therapy, bacterial resistance antibiotics, etc. [18–27].

On the other hand, it is noteworthy that, despite the outstanding therapeutic activity of *Chelidonium majus*, its overdose due to self-medication with various market herbal supplements can induce severe outcomes on liver physiological function. Therefore, avoiding this liability requires advanced herbal formulations and safety and control of dosage, leading to increased efficacy [28,29].

Accordingly, in this study, our approach to plant-derived natural products moves to a different level, using the renowned medicinal plant *Chelidonium majus* and AuNPs to achieve an innovative engineering carrier system with unique pharmacological activity.

The chemical, morpho-structural, and thermal properties; antioxidant potential; and in vitro release profile were studied systematically.

2. Results and Discussion

Numerous research studies have been conducted on the chemical composition and pharmacological activity of *Chelidonium majus*. Most of these studies have focused on specific phytoconstituent categories found in certain parts of the plant [3–8,10,30–32].

However, the plant's origin has an essential role in increasing the development of plants, as well as in triggering different defense mechanisms against various biotic factors in their environments. Among the most dominant defense systems of plants against environmental stress factors is a plant's ability to produce varied secondary metabolites and signaling molecules. Accordingly, discrepancies occur in the metabolic profiles of particular plants of different origins [17,33]. Furthermore, extraction parameters, such as solvent polarity, temperature, and pH, have a decisive impact on the phytochemical composition [34–36].

To this end, establishing a correlation between the biomolecules found in a plant and its therapeutic activity is an arduous task.

Moreover, few studies have been performed, and only on the alkaloid or phenolic contents of the Romanian *Chelidonium majus* wild plant [37,38]. Therefore, this study investigates the low metabolic profile of greater celandine using gas-chromatography coupled with mass spectroscopy (GC-MS) and electrospray ionization–quadrupole time-of-flight mass spectrometry (ESI-QTOF-MS) analysis. The phytochemicals were identified on the retention indices, in the Mass Spectral Library 2.0 database, and in the literature.

The biomolecules separated via GC-MS are presented in Figure S1 and Table 1.

Table 1. Main biomolecules identified by GC–MS analysis of *Chelidonium majus* sample.

No	Compound Name	Retention Time (RT)	Area%	Ref.
1	5-hydroxymethylfurfural	6.72	0.52	[39]
2	limonene	10.16	0.32	[40]
3	neoxanthin	15.42	18.44	[41]
4	anethole	18.91	11.13	[40]
5	sanguinarine	20.02	0.49	[42]
6	beta-carotene	21.06	0.51	[41]
7	dihydroberbine	24.53	0.36	[30]
8	chelidonine	25.12	23.48	[30]
9	dihydrosanguinarine	26.77	0.58	[30]
10	dihydrochelerythrine	29.01	2.43	[30]
11	chelerythrine	30.78	1.12	[42]
12	oxysanguinarine	31.67	27.35	[42]
13	angoline	35.89	0.47	[36]

Table 1 shows the main phytoconstituents identified via GC-MS analysis from the greater celandine sample.

The GC-MS analysis displays thirteen compounds, accounting for about 87% of the total peak area in the greater celandine sample (Figure S1).

2.1. Mass Spectrometry Analysis of *Chelidonium majus* Sample

The MS spectra (Figure S2) indicate the presence of numerous molecules, some of which were detected and assigned to different chemical classes (alkaloids, amino acids, phenolic acids, flavonoids, carotenoids, organic acids, fatty acids, sterols, and others) that corroborate the literature results [6,7,11,15,31,33,38,40,42,43].

The phytoconstituents identified via ESI–QTOF–MS analysis are presented in Table 2.

Table 2. Biomolecules identified in *Chelidonium majus* sample through MS analysis.

No	Tentative of Identification	Formula	Category	<i>m/z</i> Detected	Theoretic <i>m/z</i>	Ref.
1	acetic acid	C ₂ H ₄ O ₂	organic acid	61.07	60.05	[43]
2	glycine	C ₂ H ₅ NO ₂	amino acids	76.05	75.07	[31]
3	alanine	C ₃ H ₇ NO ₂	amino acids	90.10	89.09	[31]
4	dihydroxyacetone	C ₃ H ₆ O ₃	ketones	91.09	90.08	[43]
5	choline	C ₅ H ₁₄ NO ⁺	cholines	105.16	104.17	[11]
6	serine	C ₃ H ₇ NO ₃	amino acids	106.09	105.09	[31]
7	histamine	C ₅ H ₉ N ₃	amines	112.14	111.15	[11]
8	proline	C ₅ H ₉ NO ₂	amino acids	116.14	115.13	[31]

Table 2. Cont.

No	Tentative of Identification	Formula	Category	<i>m/z</i> Detected	Theoretic <i>m/z</i>	Ref.
9	valine	C ₅ H ₁₁ NO ₂	amino acids	118.16	117.15	[31]
10	succinic acid	C ₄ H ₆ O ₄	organic acids	119.08	118.09	[15]
11	threonine	C ₄ H ₉ NO ₃	amino acids	120.13	119.12	[31]
12	nicotinic acid	C ₆ H ₅ NO ₂	organic acids	124.11	123.11	[15]
13	5-hydroxymethylfurfural	C ₆ H ₆ O ₃	furans	127.12	126.11	[42]
14	isoleucine	C ₆ H ₁₃ NO ₂	amino acids	132.18	131.17	[31]
15	asparagine	C ₄ H ₈ N ₂ O ₃	amino acids	133.13	132.12	[31]
16	aspartic acid	C ₄ H ₇ NO ₄	amino acids	134.11	133.10	[31]
17	malic acid	C ₄ H ₆ O ₅	organic acids	135.08	134.09	[33]
18	limonene	C ₁₀ H ₁₆	terpenoids	137.23	136.23	[40]
19	tyramine	C ₈ H ₁₁ NO	amines	138.19	137.18	[11]
20	salicylic acid	C ₇ H ₆ O ₃	organic acids	139.11	138.12	[33]
21	glutamic acid	C ₅ H ₉ NO ₄	amino acids	148.14	147.13	[31]
22	anethole	C ₁₀ H ₁₂ O	anisoles	149.21	148.20	[40]
23	vanillin	C ₈ H ₈ O ₃	aldehydes	153.14	152.15	[33]
24	gentisic acid	C ₇ H ₆ O ₄	phenolic acids	155.11	154.12	[33]
25	<i>p</i> -coumaric acid	C ₉ H ₈ O ₃	phenolic acids	165.15	164.16	[33,38]
26	vanillic acid	C ₈ H ₈ O ₄	phenolic acids	169.16	168.15	[33]
27	gallic acid	C ₇ H ₆ O ₅	phenolic acids	171.13	170.12	[11,15]
28	trans-aconitic acid	C ₆ H ₆ O ₆	organic acids	175.12	174.11	[33]
29	caffeic acid	C ₉ H ₈ O ₄	phenolic acids	181.15	180.16	[15]
30	tyrosine	C ₉ H ₁₁ NO ₃	amino acids	182.19	181.19	[31]
31	chelidonic acid	C ₇ H ₄ O ₆	organic acids	185.11	184.10	[15]
32	quinic acid	C ₇ H ₁₂ O ₆	phenolic acids	193.18	192.17	[15,33]
33	ferulic acid	C ₁₀ H ₁₀ O ₄	phenolic acids	195.19	194.18	[15,39]
34	aporphine	C ₁₇ H ₁₇ N	alkaloids	236.33	235.32	[33]
35	linoleic acid	C ₁₈ H ₃₂ O ₂	fatty acids	281.41	280.40	[11]
36	oleic acid	C ₁₈ H ₃₄ O ₂	fatty acids	283.51	282.50	[11]
37	luteolin	C ₁₅ H ₁₀ O ₆	flavonoids	297.23	286.24	[11]
38	sparteine	C ₁₅ H ₂₆ N ₂	alkaloids	235.39	234.38	[11]
39	palmitic acid	C ₁₆ H ₃₂ O ₂	fatty acids	257.43	256.42	[43]
40	9-octadecenoic acid	C ₁₈ H ₃₄ O ₂	fatty acids	283.49	282.50	[43]
41	quercetin	C ₁₅ H ₁₀ O ₇	flavonoids	303.23	302.23	[11]
42	isorhamnetin	C ₁₆ H ₁₂ O ₇	flavonoids	317.25	316.26	[33]
43	coptisine	C ₁₉ H ₁₄ NO ₄ ⁺	alkaloids	321.29	320.30	[6]
44	stylophine	C ₁₉ H ₁₇ NO ₄	alkaloids	324.31	323.30	[7,11]
45	scoulerine	C ₁₉ H ₂₁ NO ₄	alkaloids	328.41	327.40	[11]
46	sanguinarine	C ₂₀ H ₁₄ NO ₄ ⁺	alkaloids	333.31	332.30	[6,11]
47	dihydrosanguinarine	C ₂₀ H ₁₅ NO ₄	alkaloids	334.29	333.30	[11]
48	berberine	C ₂₀ H ₁₈ NO ₄ ⁺	alkaloids	337.41	336.40	[6,11]
49	canadine	C ₂₀ H ₂₁ NO ₄	alkaloids	340.39	339.40	[6,11]
50	corydine	C ₂₀ H ₂₃ NO ₄	alkaloids	342.41	341.40	[11]
51	magnoflorine	C ₂₀ H ₂₄ NO ₄ ⁺	alkaloids	343.41	342.40	[11]
52	oxysanguinarine	C ₂₀ H ₁₃ NO ₅	alkaloids	348.29	347.30	[11]
53	chelerythrine	C ₂₁ H ₁₈ NO ₄ ⁺	alkaloids	349.39	348.40	[11,33]
54	dihydrochelerythrine	C ₂₁ H ₁₉ NO ₄	alkaloids	350.41	349.40	[11]
55	chelidonine	C ₂₀ H ₁₉ NO ₅	alkaloids	354.39	353.40	[6,11]
56	rosmarinic acid	C ₁₈ H ₁₆ O ₈	phenolic acids	361.29	360.30	[33]
57	dihydrochelirubine	C ₂₁ H ₁₇ NO ₅	alkaloids	364.41	363.40	[11]
58	allocryptopine	C ₂₁ H ₂₃ NO ₅	alkaloids	370.39	369.40	[6,11]
59	angoline	C ₂₂ H ₂₁ NO ₅	alkaloids	380.41	379.40	[11]
60	1-hexacosanol	C ₂₆ H ₅₄ O	alcohols	383.69	382.70	[15]

Table 2. Cont.

No	Tentative of Identification	Formula	Category	m/z Detected	Theoretic m/z	Ref.
61	sanguilutine	C ₂₃ H ₂₄ NO ₅ ⁺	alkaloids	395.39	394.40	[11]
62	dihydroberbine	C ₂₀ H ₁₉ NO ₄	alkaloids	338.41	337.40	[15]
63	chlorogenic acid	C ₁₆ H ₁₈ O ₉	phenolic acids	355.32	354.31	[11]
64	quercetol C	C ₂₂ H ₂₄ O ₅	flavonoids	369.39	368.40	[38]
65	ergosterol	C ₂₈ H ₄₄ O	sterols	397.61	396.60	[15]
66	stigmasterol	C ₂₉ H ₄₈ O	sterols	413.71	412.70	[38]
67	β sitosterol	C ₂₉ H ₅₀ O	sterols	415.69	414.70	[38]
68	nonacosanol	C ₂₉ H ₆₀ O	alcohols	425.81	424.80	[15]
69	hyperoside	C ₂₁ H ₂₀ O ₁₂	flavonoids	465.39	464.40	[11]
70	beta-carotene	C ₄₀ H ₅₆	carotenoids	537.91	536.90	[11]
71	zeaxanthin	C ₄₀ H ₅₆ O ₂	carotenoids	569.89	568.90	[11]
72	neoxanthin	C ₄₀ H ₅₆ O ₄	carotenoids	601.91	600.90	[11]
73	chlorophyll a	C ₅₅ H ₇₂ MgN ₄ O ₅	carotenoids	894.49	893.50	[11]
74	chlorophyll b	C ₅₅ H ₇₀ MgN ₄ O ₆	carotenoids	908.51	907.50	[11]

2.2. Screening and Classification of the Differential Phytoconstituents

A total of seventy-four biomolecules were identified and assigned to several categories of secondary metabolites: alkaloids (28.38%), amino acids (about 15%), phenolic acids (12.16%), flavonoids (6.75%), carotenoids (6.75%), fatty acids (5.4%), phytosterols (about 4%), terpenoids (1.75%), and miscellaneous others.

Figure 1 shows the phytochemical classification chart from the *Chelidonium majus* sample based on the data analysis reported in Table 2.

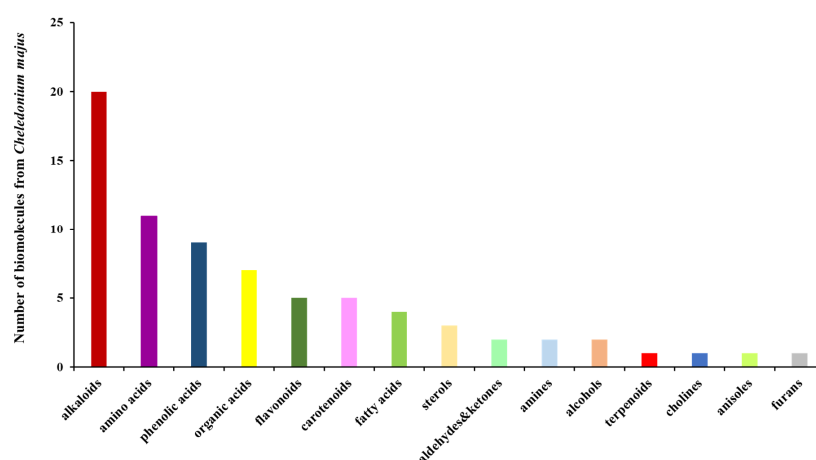


Figure 1. Biomolecule classification bar chart for *Chelidonium majus*.

According to Figure 1, alkaloids, the largest category of phytoconstituents, exhibited outstanding therapeutic activities: sedative, analgesic, antitumoral, antimicrobial, antifungal, anti-inflammatory, antidiabetic, antiemetic, antioxidant, neuroprotective, etc. [44,45].

In the greater celandine sample, eleven amino acids were identified, of which the largest percent (72.7%) was represented by non-essential amino acids (glycine, alanine, serine, proline, asparagine, aspartic acid, glutamic acid, and tyrosine). Essential amino acids (isoleucine, valine, and threonine) were present in a minor proportion (27.3%). Various research has reported the exceptional pharmacological activities of these phytochemicals (anti-inflammatory, neuroprotective, antiproliferative, cytotoxic, and immunomodulating activities [46–53]).

Phenolic acids made up about 12% of the biomolecules from the greater celandine sample, being involved in antioxidant, antimicrobial, cardioprotective, anti-inflammatory, neuroprotective, antitumor, and antidiabetic mechanisms [54].

Flavonoids (hyperoside, luteolin, quercetol, isorhamnetin, quercetin) are another secondary metabolite class with significant beneficial effects on human health (antioxidant, antimicrobial, antiviral, anti-inflammatory, antitumoral, antidiabetic, cardioprotective, hepatoprotective, and neuroprotective). In addition, luteolin is involved in the management of pain caused by anti-inflammatory disorders [55–60].

Recent research has shown that *carotenoids* exhibit antioxidant, anti-inflammatory, neuroprotective, cardioprotective, skin and eye protection, anti-obesity, antitumoral, and antimutagen activities [61,62].

Fatty acids represented 5.4% of the total phytoconstituents from the greater celandine sample. These secondary metabolites act as anti-inflammatory, antioxidant, cardioprotective, and neuroprotective agents [63,64].

Phytosterols represented 4.05% of the total phytochemicals from the greater celandine sample. These are involved in antioxidant, anti-inflammatory, immunomodulatory, anti-atherosclerotic, neuroprotective, and antitumoral mechanisms [65].

The *terpenoid* limonene displays antitumoral, antimicrobial, antifungal, antidiabetic, anti-inflammatory, antiallergenic, antitumoral (breast tumor), and neuroprotective activities [66,67].

2.3. Phyto-Nanocarrier System

Advanced nanotechnology is the key to overcoming the limitations of biomedical applications of medicinal plant preparations with high therapeutic activity. The reduced stability, permeability, and bioavailability of some specific secondary metabolites in biological environments pose significant challenges [16,17,32]. However, the engineering nanocarriers based on metallic nanoparticles offer a highly effective solution by improving biocompatibility, reducing harmful side effects, and exhibiting higher therapeutic efficiency through the synergistic effect of both components, namely, drugs and metallic nanoparticles. Moreover, these tailored nanocarriers enhance stability, permeability, targeting control, and release. Therefore, the engineering nanocarriers used in biomedical applications represent a significant advancement and are poised to have promising potential in personalized therapeutic strategies [16,68]. Accordingly, a novel phyto-carrier based on preparation of AuNPs will synergistically merge the biological activities of the *Chelidonium majus* biomolecules and metallic nanoparticles, which will achieve a higher therapeutic yield.

2.4. FT-IR and Raman Spectroscopy

Fourier transform infrared (FTIR) spectroscopy is a widely analytical technique used to obtain findings regarding molecular structure and chemical composition from complex matrices.

Hence, the preparation of the GC-AuNPs carrier system was studied using FT-IR spectroscopy to emphasize the bonding mechanism between herbs and metallic nanoparticles. FT-IR spectra are presented in Figure 2.

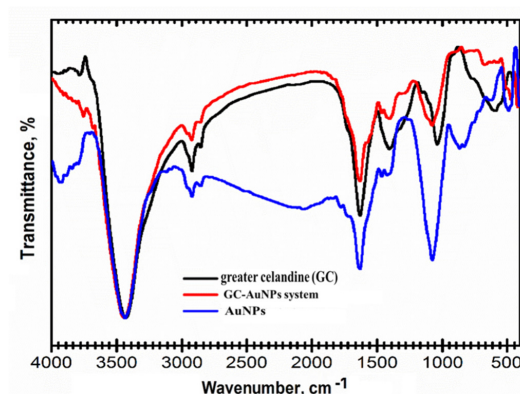


Figure 2. FT-IR overlap spectra of the carrier system of greater celandine, AuNPs, and GC-AuNPs.

The functional groups assigned to *Chelidonium majus* phytochemicals are shown in Table 3.

Table 3. The characteristic vibrational bands attributed to various biomolecule categories from the *Chelidonium majus* sample.

Biomolecule Category	Characteristic Vibrational Bands (cm^{-1})	Ref.
alkaloids	3362; 1598; 1646; 1402; 1375; 741; 663	[69]
amino acids	3380; 2358; 2128; 1751; 1675; 1665; 1649; 1632	[70]
phenolic acids	1662; 1727; 1640; 1521; 1410; 1363; 1262; 1168; 1091; 947	[18,71]
flavonoids	3234; 3082; 1655; 1618; 1583; 1465; 1415; 1372; 1274; 1079; 771; 536	[72]
fatty acids	3601; 3018; 2959; 2922; 2874; 1703; 1352; 1247; 723	[73]
carotenoids	2922; 1632; 1385; 965	[74]
phytosterols	3427; 2940; 2838; 1752; 1467; 1382; 1188; 1065; 990; 883; 742	[75,76]

The FTIR spectra of the GC-AuNPs carrier system display the characteristic absorption bands of *Chelidonium majus* (3430 cm^{-1} (-OH group), 3293 cm^{-1} (O-H stretching carboxylic acid), 1709 cm^{-1} (C=O stretching vibration), 1609 cm^{-1} (C=C of carotenoids), 1601 cm^{-1} (C=C and C=N stretching vibrations of alkaloids), 1240 cm^{-1} (C-N of amine), 1032 cm^{-1} (NH stretching of amines), and 872 cm^{-1} (C-H bending vibration of aromatic rings)), as well as the AuNPs coated with trisodium citrate (2915 cm^{-1} (OH stretching vibration); 2848 cm^{-1} (corresponding to CH- asymmetric and symmetric stretching vibrations); 1596 cm^{-1} (COO- stretching vibration); and 1392 cm^{-1} (assigned to C-H bending)), thus pointing to the successful preparation of the CG-AuNPs carrier system [18,20,69,77].

Nonetheless, the changes in the intensity of the absorption bands and the shift toward higher wavenumbers in the corresponding regions (O-H, N-H, and C-H) are noticeable and indicate their involvement in the preparation of the GC-AuNPs carrier system [20,78,79].

2.5. Raman Spectroscopy

Raman spectroscopy is an important technique that is often used to study the vibrational modes of both molecules and hybrid nanomaterials.

Figure 3 shows the characteristic Raman spectrum of the GC-AuNPs carrier system.

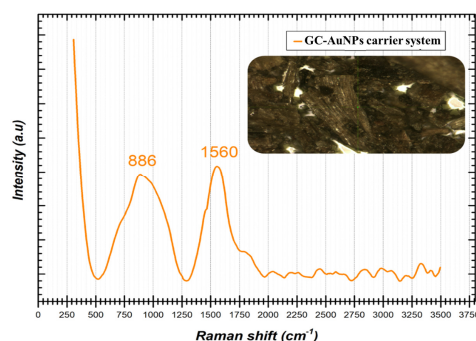


Figure 3. Raman spectrum of GC-AuNPs carrier system.

The Raman spectrum displayed in Figure 3 indicates the presence of two peak shifts identified at 886 cm^{-1} and 1560 cm^{-1} , respectively. When gold nanoparticles are subjected to Raman analysis, certain specific shifts are expected to appear in the spectrum in the ranges of $200\text{--}400\text{ cm}^{-1}$ and $500\text{--}580\text{ cm}^{-1}$ [80]. In the present case, no spectral information could be identified in the previously mentioned intervals, but the presence in the spectrum of the two Raman shifts of significantly high intensity at 886 cm^{-1} and 1560 cm^{-1} , respectively, can most probably be attributed to the vibrational modes specific to the interactions and the strong bonds between the surfaces of the AuNPs and the phytochemicals from

the greater celandine sample [7]. It is important to note that the precise shifts in the Raman spectra may vary depending on the size, morphology, and surface chemistry of the AuNPs (single or hybrid), as well as on the experimental conditions. In addition, Raman spectroscopy is often used in combination with other complementary characterization techniques, so that a more detailed understanding of the properties of gold nanoparticles and how they interact with compounds in the plant extract of celandine can be obtained.

2.6. X-Ray-Diffraction Spectroscopy (XRD)

X-Ray-Diffraction Spectroscopy (XRD) is a simple, fast, and non-destructive technique used to determine the phase composition and crystallographic data of materials [81].

Overlapped XRD patterns of the greater celandine, AuNPs, and GC-AuNPs carrier system are presented in Figure 4.

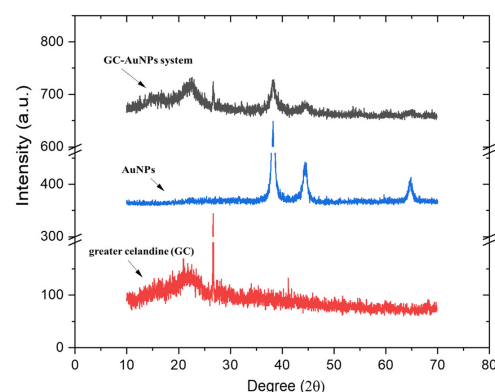


Figure 4. Powder XRD patterns of greater celandine, AuNPs, and CG-AuNPs carrier system.

The XRD spectrum of AuNPs depicts defined peaks, evidencing a well-crystalline structure, with a crystallite mean size of 17 nm, as determined using the Scherrer equation [18].

The greater celandine pattern shows amorphous phases with poorly defined peaks in the (17–43°) range, associated with minerals and plant fibers. The XRD pattern of the GC-AuNPs carrier system exhibits, even if moderately weaker, peaks of herb components and AuNPs (Figure 4), thus confirming the formation of a new carrier system.

2.7. Scanning Electron Microscopy (SEM)

The comparative analysis of morpho-structural features was carried out using the SEM-EDX method.

It appears that the SEM image of the greater celandine (Figure 5A, low magnification ($\times 850$)) indicates the presence of a fibrous structure with large pores and irregular shape agglomerations of different-sized particles (average size: ~ 30 nm). The CG-AuNPs carrier system micrograph (Figure 5B,C low magnification ($\times 850$)) indicates that AuNPs and clusters of AuNPs (spherical shape, average size ~ 17 nm) were loaded in the herb particle pores.

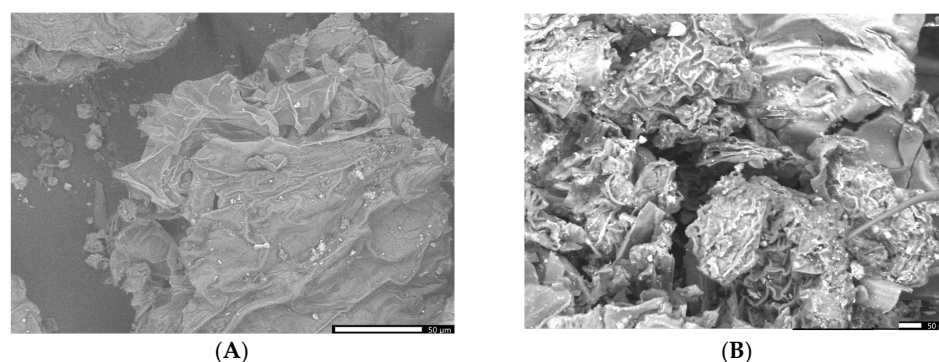
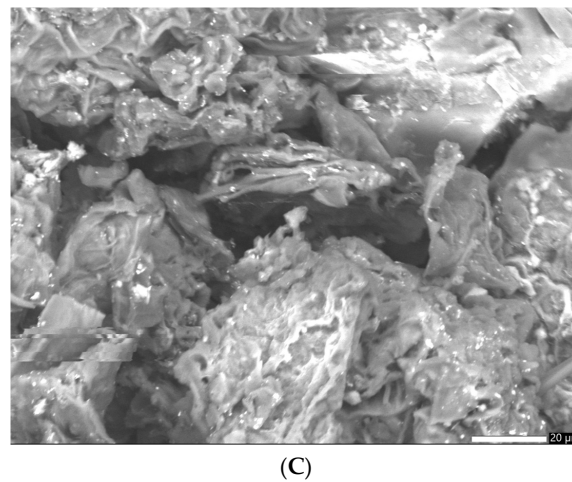


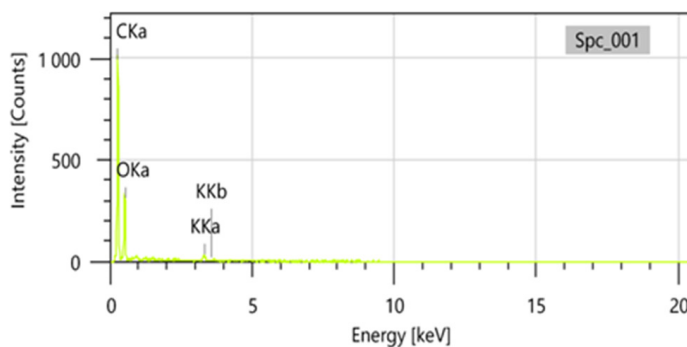
Figure 5. Cont.



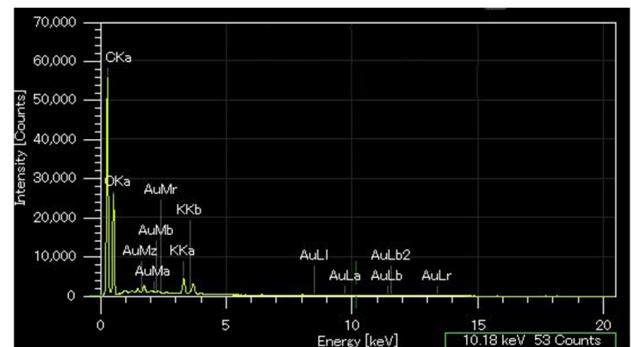
(C)

Figure 5. SEM images of the greater celandine (A) and CG-AuNPs carrier system (B,C).

The EDX analysis was carried out comparatively on the greater celandine sample and the CG-AuNPs carrier system. The EDX spectra of the new carrier system are displayed beside the peaks corresponding to greater celandine (Figure 6A) and AuNPs (Figure 6B), indicating the achievement of the CG-AuNPs carrier system.



(A)



(B)

Figure 6. EDX composition of the greater celandine (A) and CG-AuNPs carrier system (B).

2.8. Dynamic Light Scattering (DLS)

Dynamic light scattering is a routine, accurate analytic method for the mean and distribution determination of nano- and micro-scale particles in dispersion. The hydrodynamic size, distribution, and stability of the GC-AuNPs carrier system were investigated via the DLS technique. The obtained results are shown in Table 4.

Table 4. The DLS mean hydrodynamic diameter values of the GC-AuNPs carrier system and components.

Sample	Diameters (μm)	Width (μm)
greater celandine	0.9610	0.3190
	0.2555	0.1089
AuNPs	0.01675	0.0641
	1.4530	0.5040
GC-AuNPs carrier system	0.3250	0.1413
	0.0892	0.0579

The distribution of particles in solution for all samples is presented in Figure 7.

In the DLS pattern of the greater celandine sample (Figure 7A), there are two distinctive peaks corresponding to different hydrodynamic diameter values, which can be attributed to the fibrous structures and particles from the herb. According to the DLS analysis, the mean diameter of AuNPs is about 16 nm.

Conversely, the pattern of the CG-AuNPs carrier system (Figure 7C) exhibits three separate peaks, well-dispersed into a narrow range, indicating high stability. These peaks can be assigned to the presence of herb components (fibrous structures and particles) and AuNPs. It is worth noting that there was a significant shift in the sizes of AuNPs and herb components, which suggests that AuNPs were loaded into the herb pores. These findings agree with the results of the SEM study.

2.9. Thermal Properties

A comparative evaluation was conducted to determine the thermal stability of the novel carrier system and greater celandine and to identify the chemical changes. The results are presented in Figure 8.

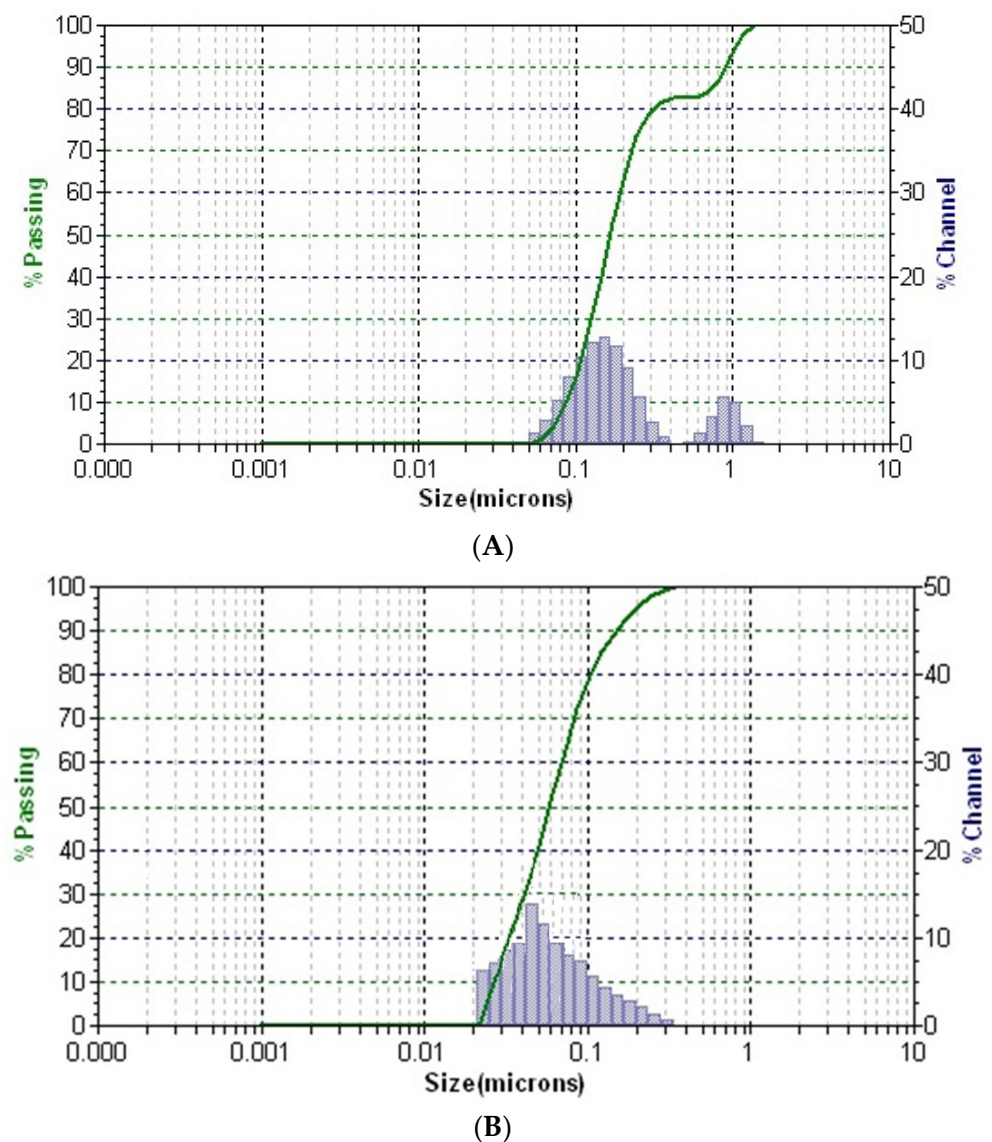


Figure 7. Cont.

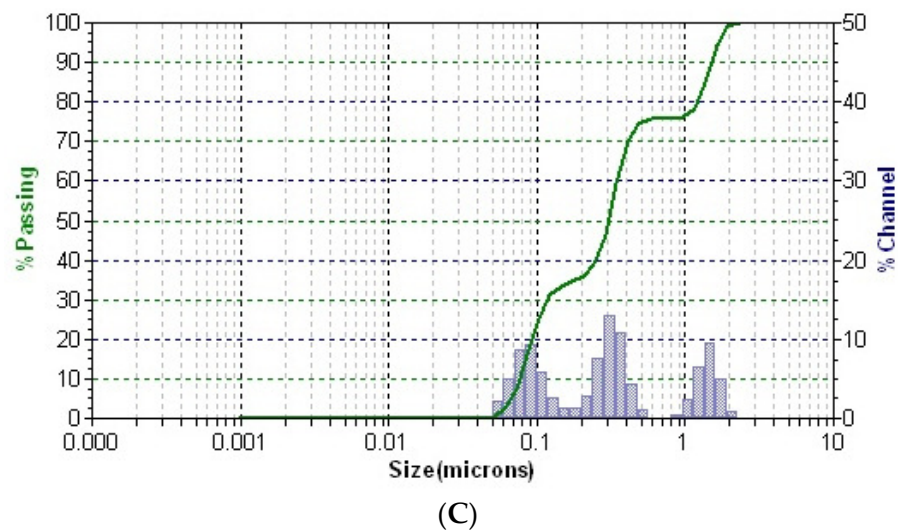


Figure 7. DLS patterns of the greater celandine (A), AuNPs (B), and CG-AuNPs carrier system (C).

The data reveal that greater celandine demonstrated an endothermic process, resulting in a substantial weight loss (55%) in the temperature range of 150–180 °C due to moisture loss and decomposition of volatile compounds, carotenoids, alkaloids, and phenolics [82,83].

Similarly, the thermogravimetric curve of the novel carrier system indicated a noticeable weight loss (46%) at 190–220 °C, assigned to phytochemical decomposition. These changes in the differential thermogravimetric curve of the new carrier system may be linked to the loading of AuNPs in the herb particles, indicating a visible increase in the thermal stability of the CG-AuNPs carrier system. The findings provide valuable insight into the behavior of these samples, and could contribute to further research and development in this field.

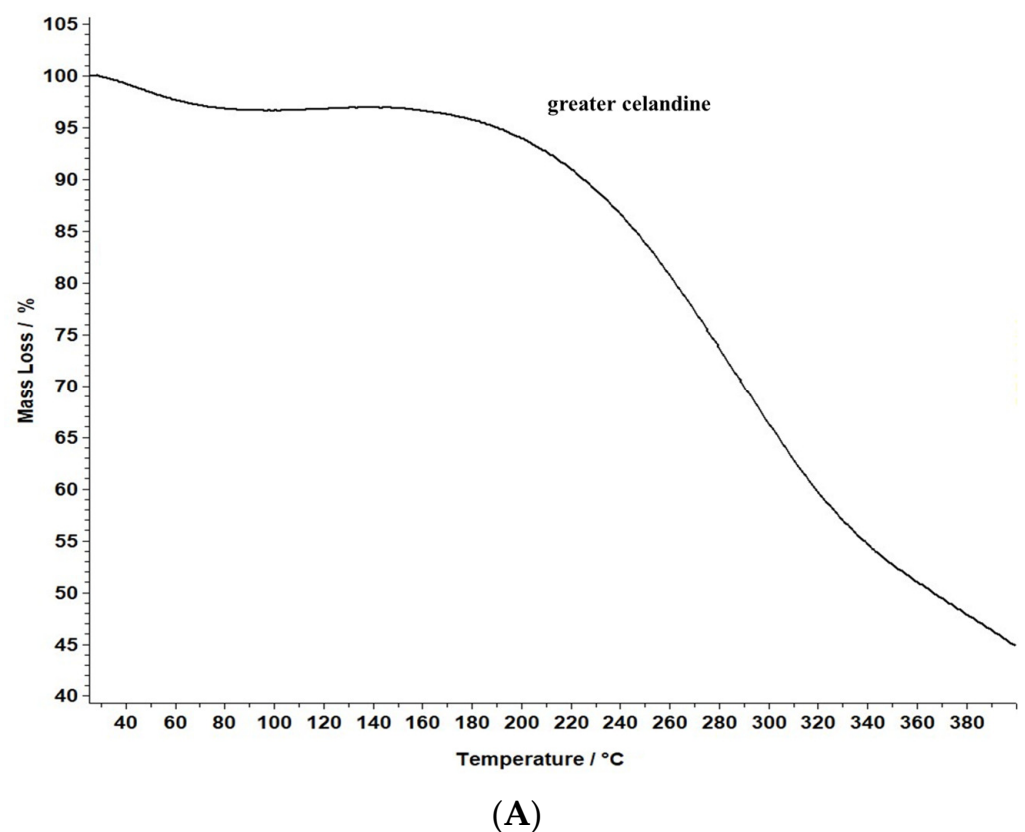


Figure 8. Cont.

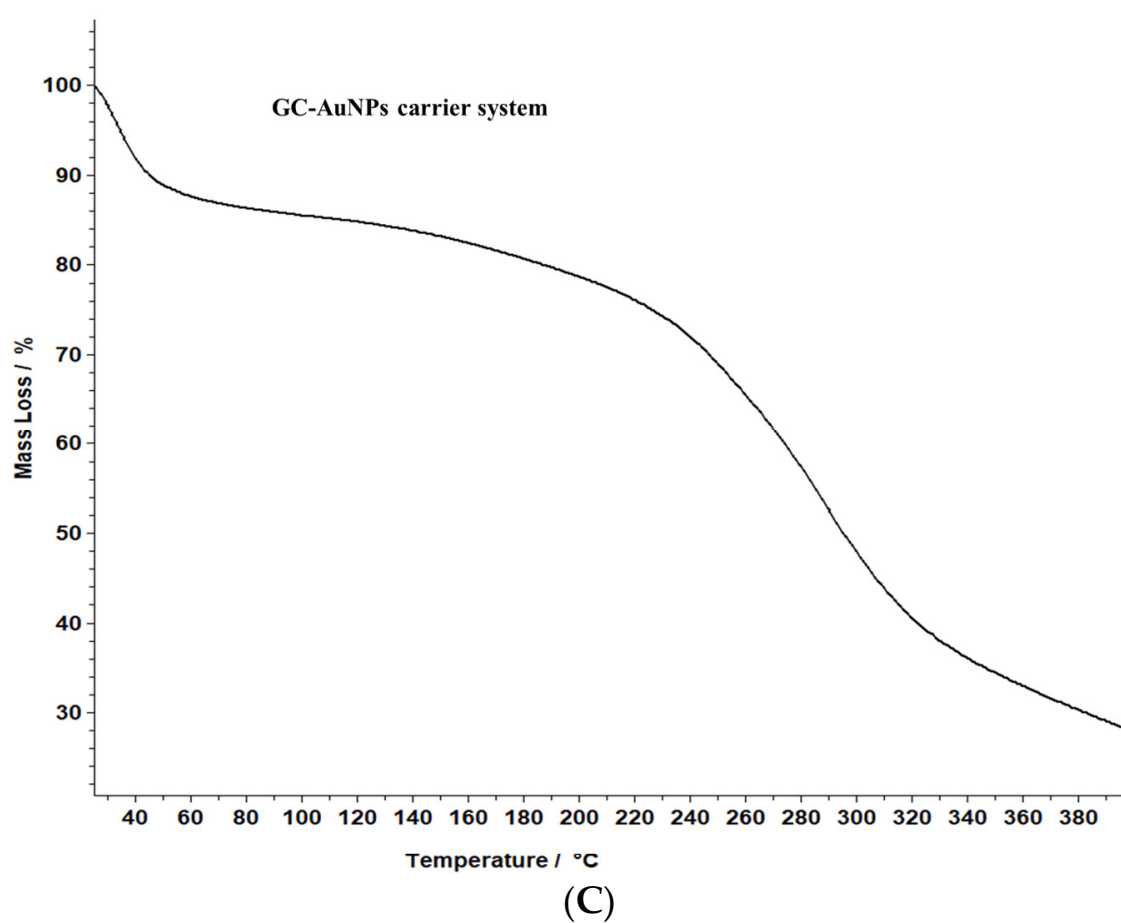
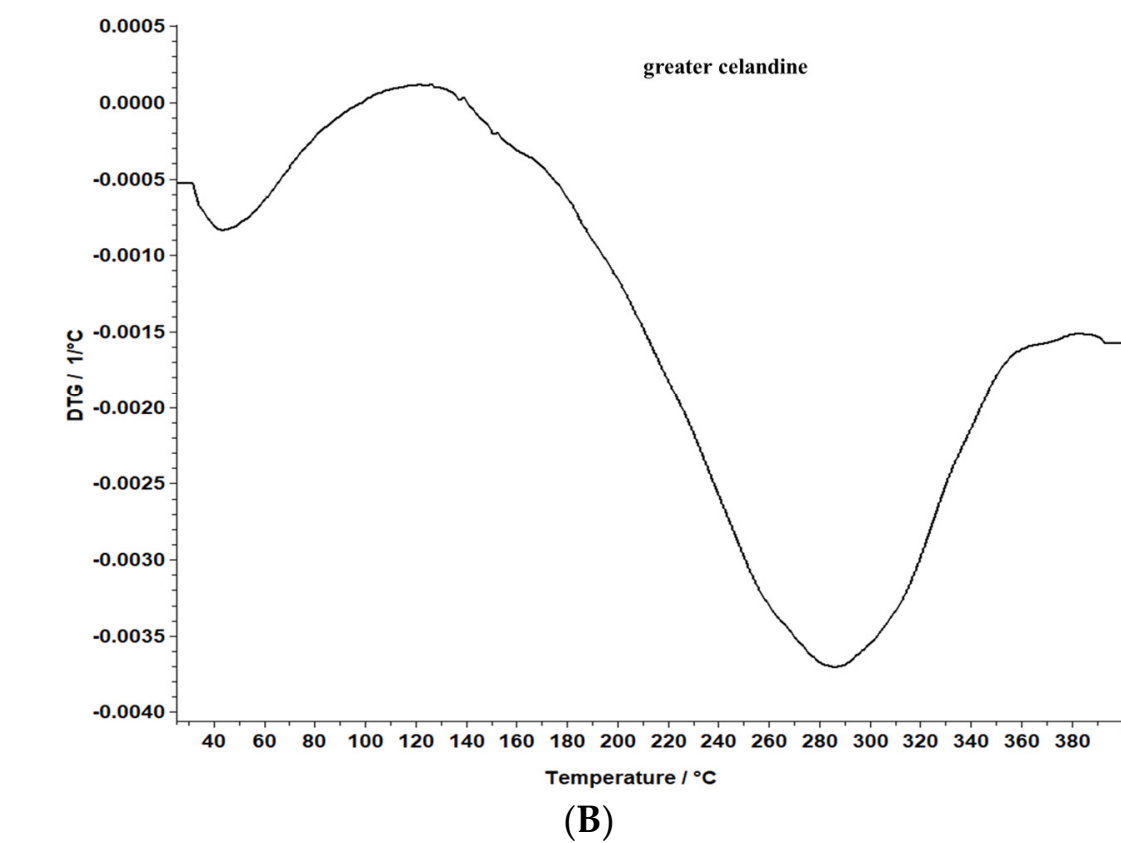


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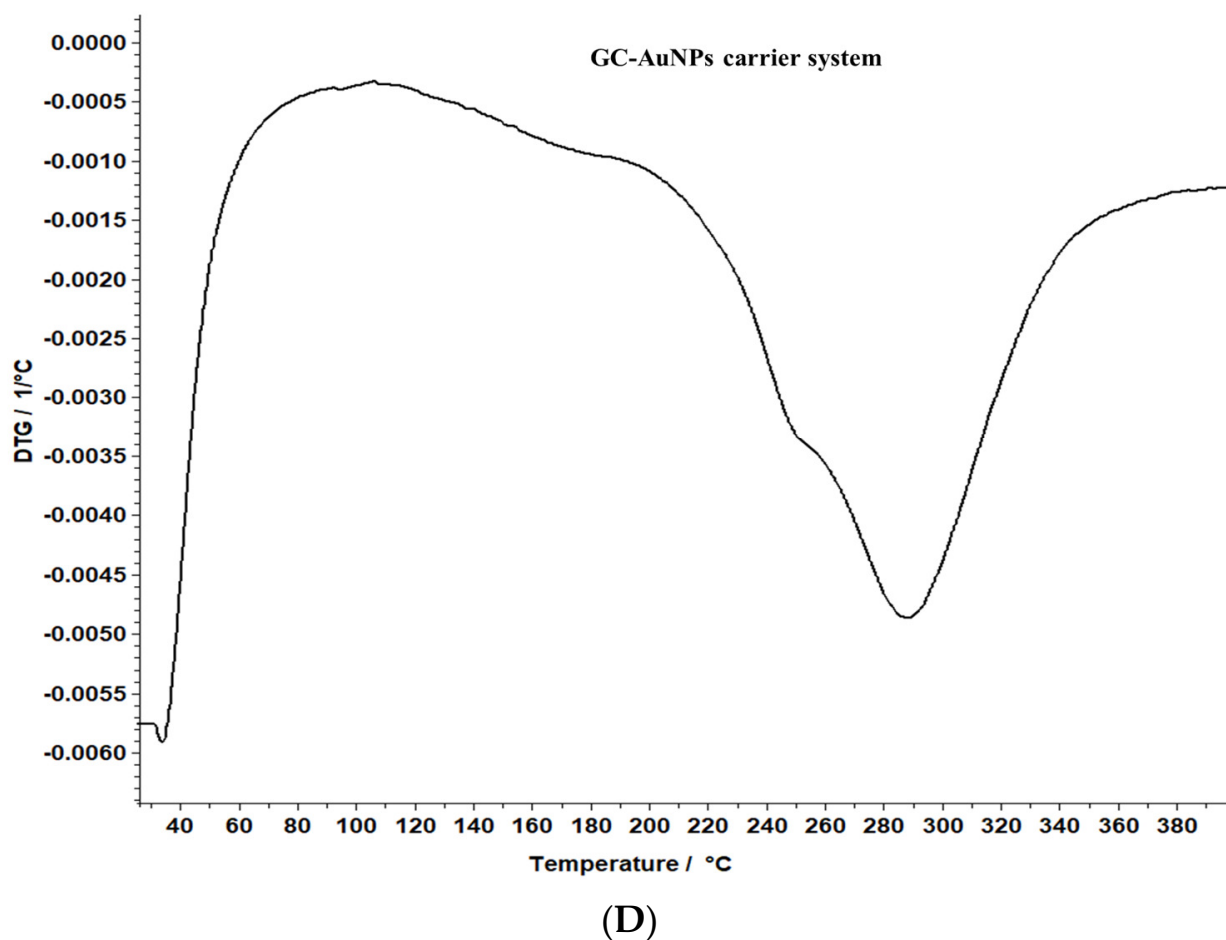


Figure 8. TG/DTG thermograms of the greater celandine sample (A,B) and CG-AuNPs carrier system (C,D).

2.10. In Vitro Dissolution Testing

In vitro dissolution assays are a ubiquitous technique in pharmacological development and quality control to predict the dissolution behavior and biological efficiency of drugs in the gastrointestinal tract [84,85]. However, due to the complex chemical composition, the bioavailability and performance assays for herbal formulations can be more challenging than for single compound products [84,85].

The pH value and time are key physiological factors with significant effects on the absorption of active biomolecules. Hence, a comparison study was performed between the dissolution profile of greater celandine and a newly prepared carrier system at pH values of 4 and 7 as a function of time.

The correlation between the pH value and dissolution rate is presented in Figure 9.

The results indicate that both samples exhibited, at pH 4, similar dissolution profiles and increased release (Figure 9A) within 30 min (over 81% for GC and over 89% for carrier system), subsequently reaching a maximum value of 93.56% for the greater celandine (Figure 9B) and 99.99% for the CG-AuNPs carrier system at 60 min. Nevertheless, at pH 7, a notable difference appeared, specifically on the dissolution profile (Figure 9C). Furthermore, even though both samples still displayed a rapid release within 30 min, these values were significantly lower than at an acidic pH (about 71% for greater celandine and 83% for CG-AuNPs carrier system) (Figure 9D). The maximum release value was reached at 60 min for the greater celandine (85.26%) and the new carrier system (94.39%).

According to the results, the novel carrier system showed notably improved bioavailability compared to the greater celandine at both pH values investigated. This enhancement can be attributed to the specific surface modification under the employed experimental conditions. Additionally, a visible reduction in the dissolution rate (approximately 5% for

the new carrier system and 8% for greater celandine) in a neutral environment (pH = 7) was observed. These unequivocal observations suggest that an acidic pH is more appropriate for the absorption of biomolecules. The findings of this study are highly significant and offer valuable insights that could significantly impact future studies on efficacy enhancement, as well as optimize the therapeutic outcome.

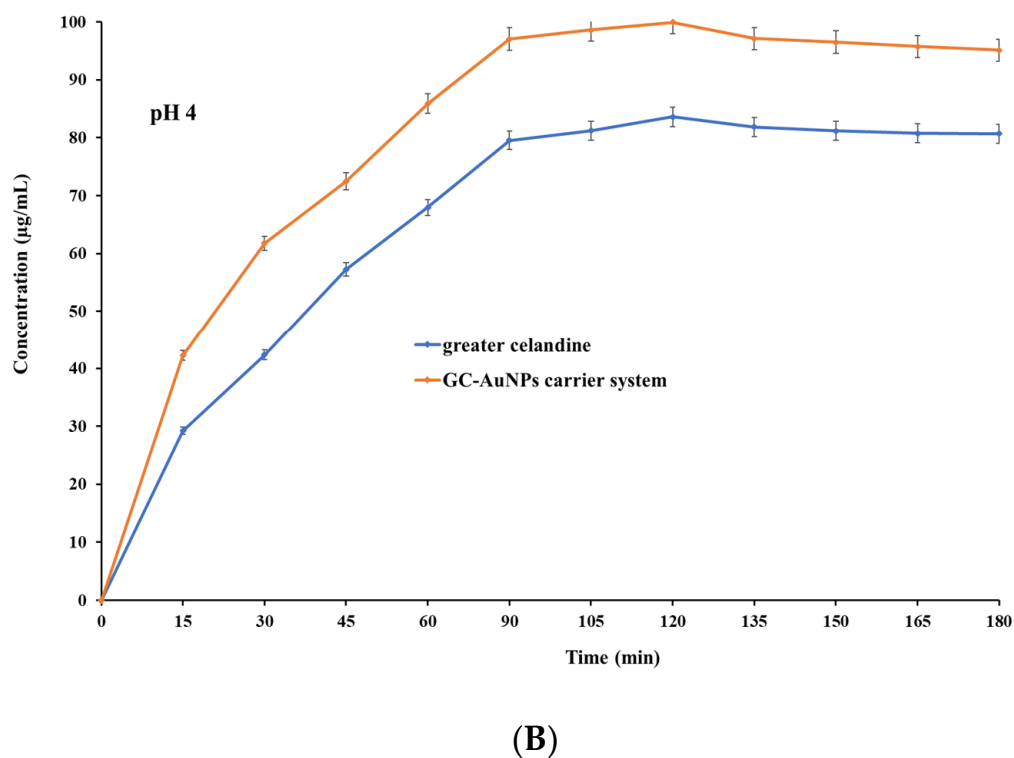
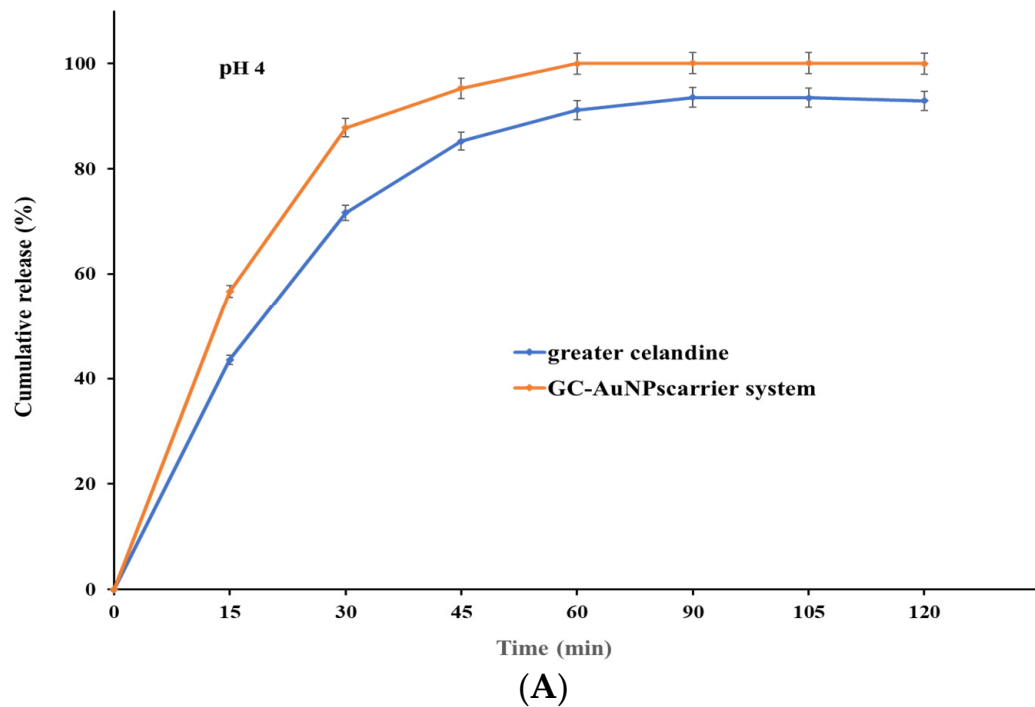
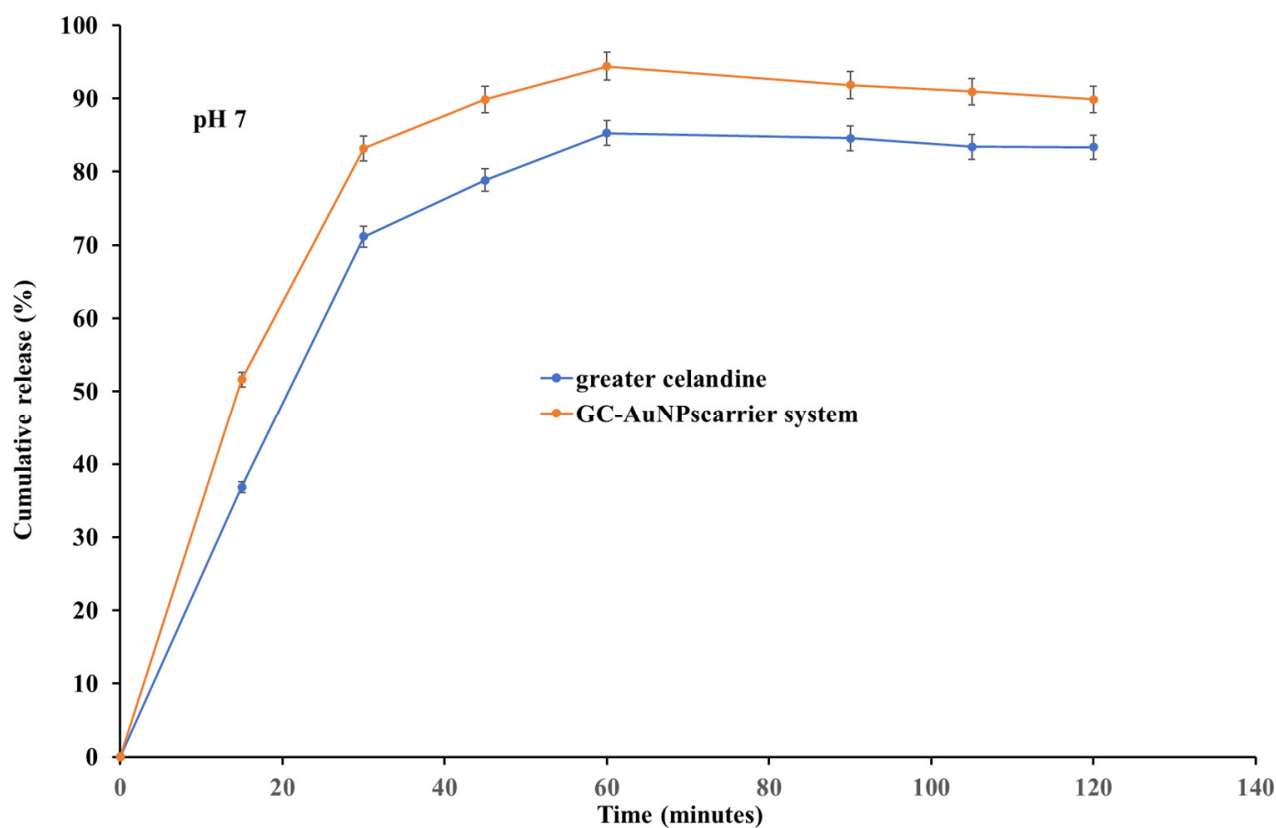
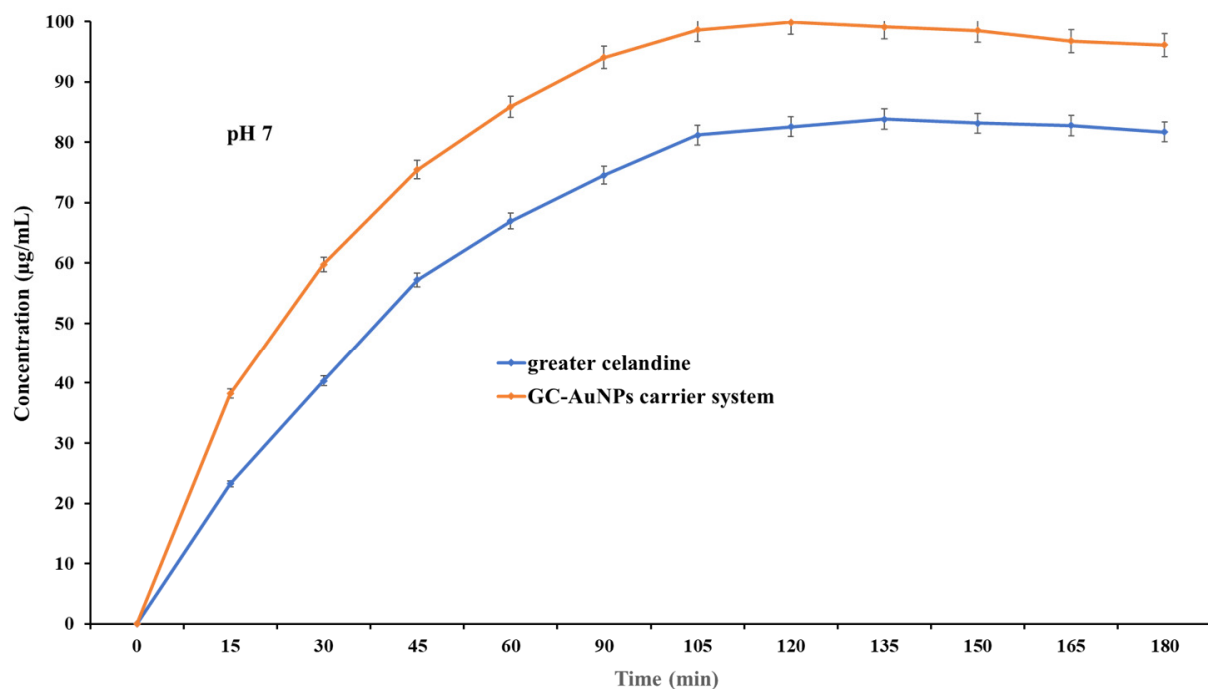


Figure 9. Cont.



(C)



(D)

Figure 9. The dissolution profile of the greater celandine and CG-AuNPs carrier system.

2.11. Screening of Antioxidant Activity

The evaluation of antioxidant potential for a specific herb formulation necessitates the selection of at least three appropriate antioxidant assays [86]. In vitro, non-competitive

assays are widely acknowledged for their simplicity and accuracy in estimating the antioxidant potential of natural products [86,87].

The antioxidant activity of a novel carrier system is attributed to a combination of collective bioactive phytochemicals from the greater celandine and the biological activity of the AuNPs. Consequently, four assays, namely, *total polyphenolic contents (TPCs)*—*Folin–Ciocalteu*, flavonoid content, FRAP, and DPPH were deemed adequate for estimating the antioxidant potential of the CG-AuNPs carrier system. The results are presented in Table 5 and Figure 10.

Table 5. The result of the selected antioxidant assay for the greater celandine and CG-AuNPs carrier system.

Sample Name	Total Phenolic Content (mg/g GAE)	Flavonoid Content (mg QE/g)	FRAP (mmol Trolox/100g dw)	IC ₅₀ (mg/mL)
GC	93.87 ± 0.028	18.48 ± 0.034	55.57 ± 0.011	53.23 ± 0.012
GC-AuNPs system	93.32 ± 0.033	19.18 ± 0.062	73.74 ± 0.014	42.78 ± 0.036

No significant differences were found in the TPCs or flavonoid assays for the novel carrier system compared to the greater celandine. However, in FRAP and DPPH tests, the CG-AuNPs carrier system exhibited higher antioxidant activity than the herb plant sample. Thus, the maximum value of the FRAP assay indicated an increase (up to 24%) for the carrier system. Similarly, the IC₅₀ value was lower than that of the greater celandine by over 24%. These results can be attributed to modifications in the surface electric charge of metallic nanoparticles loaded into herb particles, as well as the synergistic action of AuNPs and the bioactive phytoconstituents [88,89].

This assay selection offers a comprehensive evaluation of the antioxidant potential of the carrier system, which is vital for the development of effective and safe antioxidant formulations [20,90].

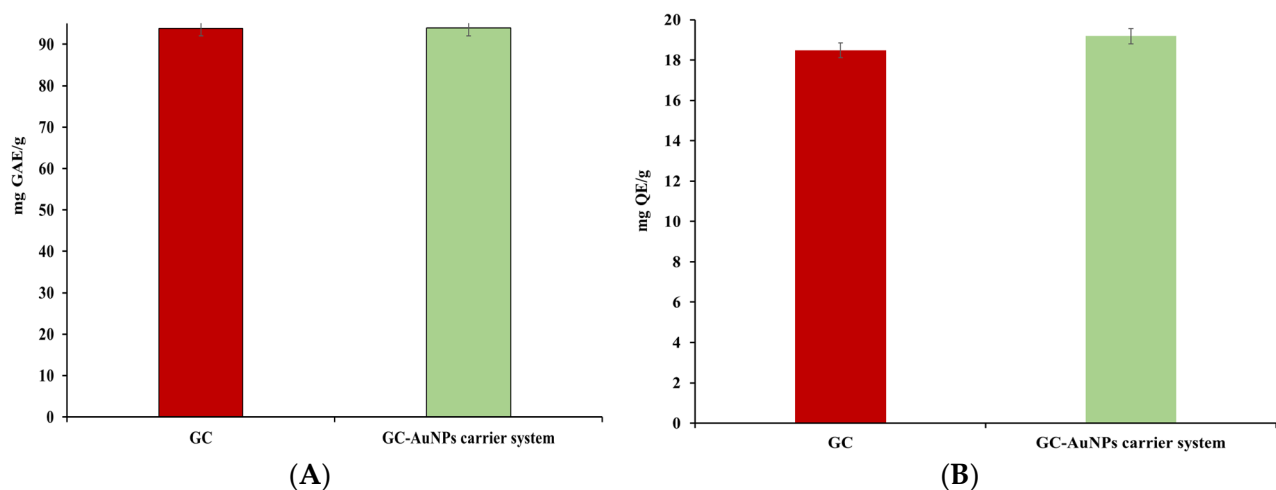


Figure 10. Cont.

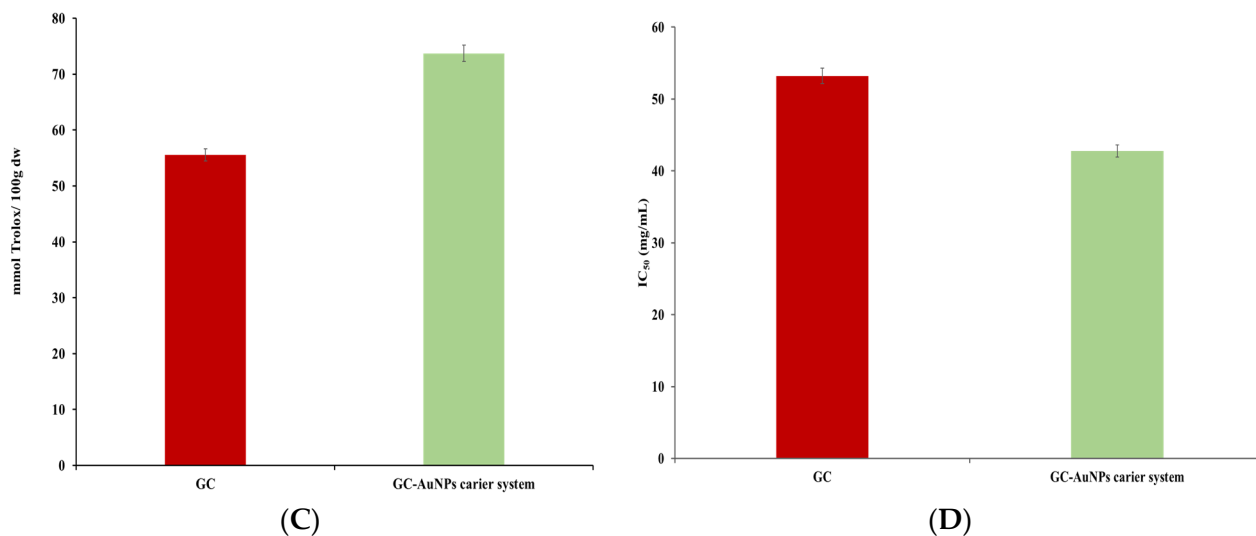


Figure 10. Graphic representation of total phenolic (A), flavonoid content (B), FRAP (C), and DPPH (D) results.

3. Materials and Methods

All reagents were of analytical grade, purchased from commercial sources (Merck Millipore (Darmstadt, Germany), Sigma-Aldrich (München, Germany)), and used without further purification.

Chelidonium majus (greater celandine) samples (whole plant) were harvested in August 2023 from the area of Hunedoara County, Romania (geographic coordinates 45°43'04"N 22°53'13"E), and taxonomically authenticated at the University of Medicine and Pharmacy Craiova, Romania.

3.1. Plant Samples' Preparation for Chemical Screening

The greater celandine samples underwent milling via a planetary Fritsch Pulverisette mill (Idar-Oberstein, Germany) (700 rpm for 10 min at 22 °C), followed by sieving through ASTM sieves. Only particles that passed through a 0.25 mm mesh sift were used in this study. Then, the plant samples were subjected to ultrasonic-assisted extraction (Elmasonic, Singen, Germany) under specific temperature, time, and ratio conditions (25 min, at 40 °C and 50 Hz, in methanol: chloroform = 1:1, *v/v*). The resulting extract was concentrated using a rotary evaporator, dissolved in MeOH (10 mL), centrifuged, and filtered. Subsequently, the extract samples were stored in a freezer until further use. All experiments were prepared in triplicate.

3.1.1. GC-MS Analysis

Gas chromatography was carried out using a GCMS-QP2020NX Shimadzu apparatus with a ZB-5MS capillary column (30 m × 0.25 mm id × 0.25 µm) (Agilent Technologies, Santa Clara, CA, USA) and helium (flow rate of 1 mL/min.)

GC-MS Separation Conditions

The oven temperature was increased from 50 °C (kept for 2 min) to 300 °C (rate of 4 °C/min, hold for 5 min). The temperature of the injector was 290 °C, and the temperature at the interface was 217 °C. The mass of the compounds was registered at 70 eV of ionization energy. The mass spectrometer was source-heated at 225 °C, and the MS Quad was heated at 155 °C. Phytochemicals were identified based on their mass spectra compared to the NIST0.2 mass spectra library database (USA National Institute of Science and Technology software, (NIST, Gaithersburg, MD, USA) and the literature review.

3.1.2. Mass Spectrometry

The MS experiments were performed using an EIS-QTOF-MS (Bruker Daltonics, Bremen, Germany). The mass spectra were acquired in positive ion mode in a mass range of 50–3000 m/z . The scan speed was 2.1 scans/s, the collision energy was 10 ÷ 85 eV, and the temperature of the source block was 80 °C. Compounds were identified based on their mass spectra, then compared to the NIST 3.0 database mass spectra library database (USA National Institute of Science and Technology software) (NIST, Gaithersburg, MD, USA) and the literature review.

3.2. CG-AuNPs Carrier System Preparation

3.2.1. The synthesis of AuNPs was achieved according to the *procedure* described in our earlier publication [18]

3.2.2. CG-AuNPs Carrier System

The greater celandine sample (whole plant dried) and AuNPs solution were mixed (1:2.5 mass ratio) under continuous stirring for 6 h at room temperature (22 °C). The emerging suspension was centrifuged, filtered, and then dried at 40 °C for 6 h. Each experiment was repeated three times.

3.3. Characterization of Novel Carrier System and Raw Materials

3.3.1. Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectra of the CG-AuNPs carrier system and its components in the solid phase were recorded on a Fourier transform infrared spectrometer (Shimadzu AIM-9000 with ATR devices).

3.3.2. XRD Spectroscopy

Data on the phase composition were obtained on a Bruker AXS D8-Advance X-ray diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) equipped with a rotating sample stage; an Anton Paar TTK low-temperature cell (−180 °C ÷ 450 °C); a high-vacuum, inert atmosphere; and relative humidity control. The average crystallite size and phase content were determined using the whole-pattern profile-fitting method (WPPF).

3.3.3. Scanning Electron Microscopy (SEM)

Morpho-structural investigations were carried out using an SEM-EDS system (JEOL JSM-IT200 Field Emission, Nieuw-Vennep, The Netherlands) equipped with a high-resolution electron gun and an energy-dispersive X-ray spectrometer (EDS).

3.3.4. Dynamic Light Scattering (DLS) Particle Size Distribution Analysis

The DLS analysis was conducted with a scattering angle of 172 °C at room temperature (22 °C) using a Microtrac/Nanotrac 252 (Montgomeryville, PA, USA) instrument. Each experiment was repeated three times.

3.3.5. Thermal Analysis

The thermal stability study of the novel carrier system and herb sample was performed in a dynamic air atmosphere (20 mL/min, synthetic air) at a temperature range of 25 ÷ 400 °C and a heating rate of 10 °C/min using a Thermal Analyzer produced by METTLER TOLEDO, model TGA/DSC3+ STARe System. The DSC analysis was performed in an air atmosphere (50 mL/min), at a temperature range of 25–400 °C, on a DSC 3+ Mettler Toledo.

3.4. Antioxidant Activity

In vitro antioxidant potential screening of the novel carrier system and herb sample were examined using four distinct tests: Folin–Ciocalteu assay; flavonoid content assay; 2,2-diphenyl-1-picrylhydrazyl; (DPPH) radical scavenging assay; and ferric reducing antioxidant power assay (Frap).

3.4.1. Folin–Ciocalteu Assay

The antioxidant activity of *Chelidonium majus* and GC-AuNPs was determined using UV-VIS spectrophotometry (DLAB SP-UV1000, Penjuru, Singapore), according to the experimental procedure described in the literature [91]. The results are expressed in gallic acid equivalents (mg GAE/g sample). Sample concentrations were calculated based on the linear equation obtained from the standard curve ($y = 0.0015x + 0.2134$) and the correlation coefficient ($R^2 = 0.9971$).

3.4.2. The Flavonoid Content Assay

The flavonoid contents from both samples were determined according to the experimental procedure adapted from the literature [92].

The absorbance was measured at 510 nm using a UV-Vis spectrometer (DLAB SP-UV1000). The flavonoid content was expressed in quercetin equivalents (mg QE/g) using a quercetin standard calibration curve between 12.5 mg/mL and 100 mg/mL in methanol. Sample concentrations were calculated based on the linear equation obtained from the standard curve ($y = 0.0083x + 0.1114$) and the correlation coefficient ($R^2 = 0.9961$).

3.4.3. Ferric Reducing Antioxidant Power Assay (FRAP)

The ferric reducing/antioxidant activity (FRAP) of the sample was determined spectrophotometrically using a Ferric Reducing Antioxidant Power (FRAP) Assay Kit (MAK369-1KT, Sigma-Aldrich). The absorbance was measured at 594 nm using a UV-Vis spectrometer (Elabsience®, Houston, TX, USA). The results were expressed in Trolox equivalents (mmol Trolox equivalents/100 g dry weight (dw)).

3.4.4. DPPH Radical Scavenging Assay

The radical scavenging properties of the novel carrier system and herb sample were assessed according to the procedure described in our earlier publication [93]. The results were used to calculate and obtain the IC_{50} (mg/mL).

All experiments for antioxidant activity screening were performed in triplicate.

3.5. In Vitro Dissolution Test

The dissolution profiles of the greater celandine ($0.5 \text{ g} \pm 0.012$) and CG-AuNps carrier system ($0.5 \text{ g} \pm 0.016$) were determined using a 708-DS Dissolution-Agilent Technologies (Santa Clara, CA, USA). The tests were conducted under strict conditions: a temperature of 37 ± 0.25 °C, a speed of 100 rpm, and two buffers of pH 4 and pH 7, respectively, to simulate the gastric and intestinal fluids [94].

Sink conditions were rigorously maintained throughout the test.

During the experiment, samples of dissolution medium (5 mL) were collected at different times (15–120 min). The cumulative drug released against time was determined spectrophotometrically (UV-Vis Perkin-Elmer Lambda 35 (Perkin Elmer, Waltham, MA, USA)).

Triplicate samples were analyzed at each time point. The mean values of the samples and the standard deviation were calculated [95].

Preparation of the Curves of the Concentrations for the Compound Dissolution Profile

Different solution concentrations (in the range of 0.00 and 0.30 mg/mL) were prepared from each sample (greater celandine and CG-AuNP carrier system, respectively). Then, calibration curves were plotted. The amount of compound released was obtained from the standard curve of the concentration versus its absorbency. The correlation coefficients at pH = 4 were: $R^2 = 0.9978$ (greater celandine) and $R^2 = 0.9986$ (CG-Au NPs carrier system), and at pH = 7, $R^2 = 0.9991$ (greater celandine) and $R^2 = 0.99984$ (CG-Au NPs carrier system). This demonstrates the good linear relationship of the data.

The compound release was calculated according to Equation (1) [96]:

$$CDR (\%) = \frac{\text{amount of released compound at time } n \text{ (g)}}{\text{amount compound used as raw materials (g)}} \times 100 \quad (1)$$

3.6. Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics 21.0 for Windows (SPSS Inc.). Each experimental set was performed in triplicate, using one-way analysis of variance (ANOVA) without replication with Scheffe's post hoc test for comparison; $p < 0.05$ was taken as statistically significant. Data are presented as the means $\pm$ SD.

4. Conclusions

This study presents the low-molecular-mass-metabolite profiling of *Chelidonium majus* growing wild in Romania, followed by the development and in vitro evaluation of the antioxidant and release of a novel carrier system prepared using this medicinal plant and AuNPs. Various analytical methods, including FTIR, Raman, XRD, DLS, and SEM-EDX, were employed to confirm the preparation of the carrier system. The TG/DTG study results demonstrated that the GC-AuNPs carrier system had superior thermal behavior compared to the herb sample. The study indicates that this novel carrier system had significantly enhanced antioxidant activity and an improved release rate. These results suggest its auspicious potential as a promising candidate for various applications.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/plants13050734/s1>, Figure S1: TIC chromatogram of *Chelidonium majus* sample.; Figure S2: The mass spectra of *Chelidonium majus* sample.

Author Contributions: Conception and design of the study: A.-E.S.; methodology: A.-E.S., L.E.B., S.B., G.V., T.V., M.-V.C. and C.B.; analysis and interpretation of data: G.V., T.V., M.-V.C., A.D., G.B. and E.R.B.; writing—original draft preparation: S.B.; writing—review and editing: A.-E.S.; investigation: G.V. and T.V acquisition of data.; M.-V.C., A.D., G.B. and E.R.B. All authors have read and agreed to the published version of the manuscript.

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