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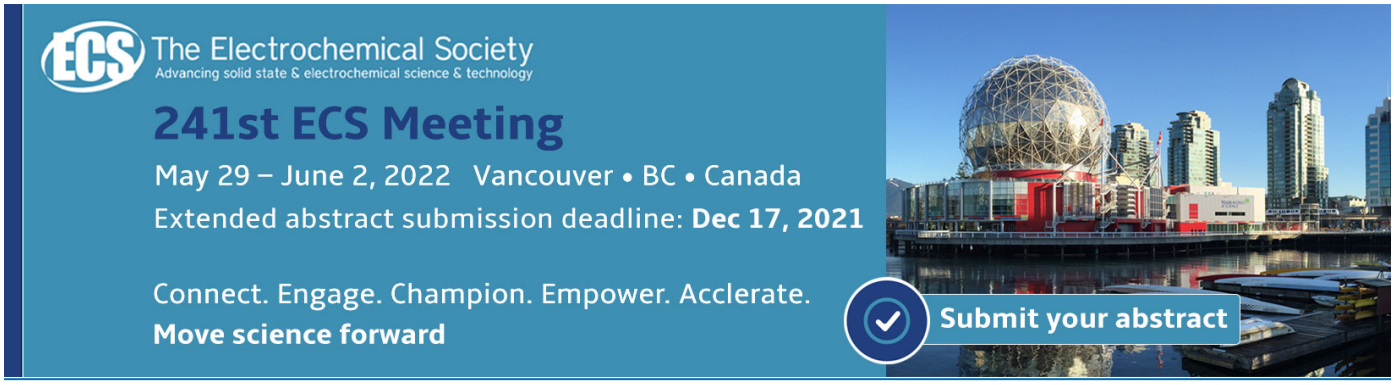

Extraction of phenolic compounds from Iraqi *Coriandrum Sativum* L. and loaded on copolymeric hydrogels and examine there as drug delivery system and antioxidant

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Abstract. The phenolic extracts for leaves and stems (L+S) parts and leaves (L) part of Iraqi *Coriandrum Sativum* L. and their total phenols, total tannins and total flavonoids are described. Three copolymeric hydrogels prepared and loaded with phenolic extract 4 (U1-U3). The HPLC results show three phenolic compounds, while the GC-Mass results show one phenolic compound and four non-phenolic compounds. Gained results showed that there are significant ($P < 0.05$) variations in total phenols (9.822 ± 0.634–4.015 ± 0.118 mg GAE/g DW), total flavonoids (8.112 ± 0.115–2.811 ± 0.371 mg QE/g DW) and total condensed tannin (4.245 ± 0.276–1.135 ± 0.091 mg QE/g DW) contents for all phenolic extracts. The swelling rate for (U1-U3) in distilled water, the SGF, and the SIF was estimated. The maximum swelling was observed in copolymeric hydrogels at pH 6.9 in distilled water. The IC_{50} values of radical scavenging activity of the phenolic extracts 4, 8 and phenolic extract 4 released from copolymeric hydrogels (U1-U3) show varied significantly ($P < 0.05$). Our results indicated that Iraqi *Coriandrum Sativum* L. could constitute a rich and novel source of natural antioxidants. When it loaded on, copolymeric hydrogels could be used as a drug delivery system.

1. Introduction

Medicinal plants are necessary due to having bioactive compounds like phenolic compounds applied in the manufacture and development of drugs [1]. Phenolic compounds in plants already proved beneficial effects in cardiovascular diseases, diabetes, cancer, anti-inflammatory effects [2], and antioxidant activities. They have been proved to be more potent antioxidants than vitamins E and C and carotenoids [3] [4, 5]. Antioxidants can inhibit the oxidation processes called oxidative stress caused by oxygen or reactive oxygen species (ROS). The main problems of oxidative stress in cells were damaging proteins, lipids, and DNA [6]. Phenolic compounds have high antioxidant activity due to their phenoxyl radicals that could stabilize the whole structure through resonance when reacting with oxidants [7].

Coriandrum sativum L. is an annual medicinal herb belonging to the Apiaceae family. It uses many issues such as to treat loss of appetite, convulsion, anxiety, and insomnia [8], antioxidant [9-11], antifungal [12, 13], antibacterial [14, 15], diuretic [16], antidiabetic [17, 18], cancer chemopreventive activities [19],

exhibits anxiolytic properties and a sedative effect [20, 21], and provides significant protection from heart failure [22].

Hydrogels are a class of three-dimensional (3D) hydrophilic polymeric network. Polymeric structures can swell in water and biological fluid and keep water and biological fluids in the swelling state due to hydrophilic groups' presence in gel structure (e.g., $CONH_2$, -COOH, -OH, $-SO_3H$) that absorbs water and keeps it inside the hydrogel chains. They are having many applications, such as drug delivery [23], gene delivery [24], tissue engineering [25], and wound healing [26]. The oral drug delivery system is the most appropriate method in many clinical trials. The hydrogels as drug delivery are excellent due to swelling in water, permeable of the solute through the pores, the controlled release systems and reducing side effects and toxicity within the organism's body [23]. To date, there is a good idea to develop an integrated approach for developing bioapplications using polymers hydrogels to carry the natural bioactive compounds extracted from plants. In the present study, eight phenolic extracts for leaves and stems (L+S) parts and leaves (L) part of Iraqi *Coriandrum Sativum* L. were prepared. Then, the total phenols, total tannins, total flavonoids and antioxidant capacities were examined. Three copolymeric hydrogels loaded with phenol extract 4 of *Coriandrum Sativum* L. (U1-U3) *via* redox polymerization were prepared. It is best to know that there are no reports on the loaded phenol extract on hydrogels and studies it as a drug delivery system and antioxidant.

2. Materials and Methods

2.1. Chemicals

Chemicals used in this study were obtained from different sources. Absolute ethanol and methanol were supplied from V.W.R. Acryl amide, 2-Acrylamido-2-methylpropane sulfonic acid, DMSO, and sodium chloride was supplied from Merck, Germany. BHT, DPPH, quercetin, N, N\-Methylenebis(acrylamide), and Potassium hydroxide were supplied from Sigma Aldrich, Germany. Sodium carbonate, Vanillin was delivered from Alpha. Sodium nitrite, sodium persulfate, sulfuric acid, N, N, N\,N\Tetramethyleneethylendiamine were supplied from Fluka**.** Potassium dihydrogen phosphate was supplied from H.W. Sodium hydroxide, Folin–Ciocalteu reagent were supplied from HIM. Aluminium chloride was supplied from B.D.H. Gallic acid was supplied from M.N.B.

2.2. Plant material and extracts preparation

The fresh leaves and stems of *Coriandrum Stavium* L. were collected from a local market in Basrah city, Iraq, in September 2019. They were classified in the Department of Biology, Faculty of Science, University of Basrah, Basrah, Iraq. These parts were manually divided into two groups; the leaves (L) part and the mixture of leaves and stems (L+S) part, cleaned, washed with distilled water, dried away by the direct sunlight, and then ground into powder an electrical grinder. The powder was kept in a closed container at 7°C until the time of use. Eight phenolic extracts were prepared, two groups were divided, and four groups of leaves and steams mixture (L + S) and four groups of leaves (L) were used with both ethanol and methanol solvent and stirred at different times. The extracts were prepared by the modified method [27]. Three g of dry powder sample was separately extracted by stirring with 30 mL of solvent for a specific time, and the extracts were kept for 24 h at 4°C, filtered through a Whatman paper No.6, then dried and stored until use. See table 1.

2.3. Total phenols content

Total phenols contents were tested using the Folin–Ciocalteu reagent by following slightly modified literature Singleton's method [28]. An aliquot 0.125 mL of convenient diluted phenolic extracts were taken in a test tube and added to 0.5 mL of deionized water and 0.125 mL of the Folin–Ciocalteu reagent. The mixture was shaken and allowed to stand for 6 min before adding 1.25 mL of 7% Na_2CO_3 solution. The

solution was then adjusted with deionized water to a final volume of 3 mL and mixed thoroughly. After incubation for 90 min at 23°C, the absorbance versus prepared blank was read at 760 nm. Gallic acid was used as the standard. The total phenol amount was calculated using the standard curve of gallic acid drawn within a concentration range of 0.2 to 1 mg/mL had an R^2 value of 0.994. It was expressed as mg gallic acid equivalents g^{-1} (mg GAE g^{-1}) leaves and stems. All samples were performed in duplicate.

Table 1. Preparation of the extracts of *Coriandrum Stavium* L leaves and stems mixture (L+S) and leaves (L) using methanol and ethanol solvent.

No. of extract	Type of part used from the plant	Solvent	Time of stirrer
1	Leaves and stems (L+S)	Methanol	30 min
2	Leaves and stems (L+S)	Methanol	24 h
3	Leaves and stems (L+S)	Ethanol	30 min
4	Leaves and stems ((L+S	Ethanol	24 h
5	Leaves (L)	Methanol	30 min
6	Leaves (L)	Methanol	24 h
7	Leaves (L)	Ethanol	30 min
8	Leaves (L)	Ethanol	24 h

2.4. Total flavonoid content

Total flavonoid contents were measured in line with the slightly modified literature method described by [29]. A 250 µL of phenolic extracts was briefly taken in a test tube mixed with 75 µL $NaNO_2$ (5%). After 6 min, 150 µL of 10% $AlCl_3$ and 500 µL of NaOH (1M) were added to the mixture. Finally, the mixture was adjusted to 2.5 mL with distilled water. The absorbance versus prepared blank was read at 510 nm on a UV spectrophotometer. Total flavonoid contents of all extracts (two replicates per treatment) were expressed as mg quercetin equivalents per gram (mg QE/g) using a standard curve of quercetin drawn within a concentration range of 0.2 to 1 mg/mL had an R^2 value of 0.986.

2.5. Condensed tannin content

In concentrated H_2SO_4, condensed tannins were turned by vanillin's reaction into anthocyanidols by following a slightly modified literature method [30]. Fifty µL of the phenolic extract appropriately diluted was taken in a test tube and mixed with 3 mL of 4% methanol vanillin solution and 1.5 mL of H_2SO_4. After 15 min, the absorbance was measured at 500 nm. Condensed tannin contents of all extracts (two replicates per treatment) were expressed as mg quercetin equivalents per gram (mg QE/g) using a standard curve of quercetin drawn within a concentration range of 0.2 to 1 mg/mL had an R^2 value of 0.987. duplicate measurements were taken for all samples.

2.6. Hydrolysis and identification of phenolic compounds using HPLC and GC-MS

The two dried samples of leaves and stems mixture (L+S) and leaves (L) for *Coriandrum Sativum* L. were acidic hydrolyzed according to modified literature method [31] to show the phenolic composition by GC/MS and HPLC. The acidic hydrolysis was followed to remove the aglycones. That will help identify the samples

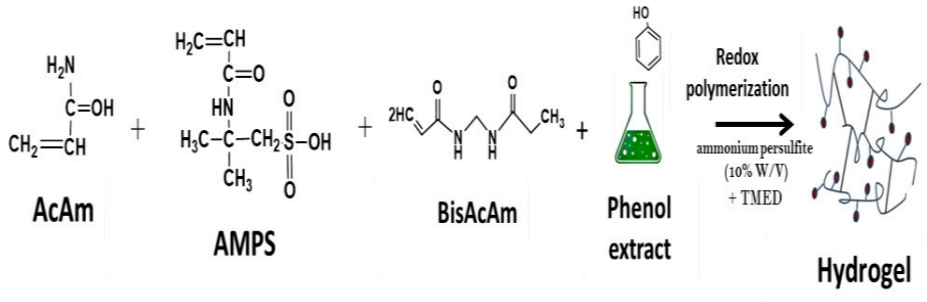
(L+S) and (L) simply due to the plants' phenolic compounds found as glycosides esters or bound to the cell wall. They are rarely present as free forms [32]. Twenty mL of methanol containing BHT (1 g/L) was added to 0.5 g of a dried sample. Then 10 mL of 1 M HCl was added. The mixture was stirred carefully and sonicated for 15 min and refluxed in a water bath at 90°C for 2 h. The obtained mixture was injected into HPLC and GC-MS.

2.6.1. Gas Chromatography-Mass Spectroscopy. Gas Chromatography-Mass Spectrometry (GC-MS) analysis was performed in Tehran University, Iran, by an Agilent 7890A\GCMS (USA). An instrument using a Hp 25 column and 1µL of each dried samples dissolved in ethanol was injected in the following conditions: injector temperature, 300°C; carrier gas, helium; pressure, 11.962 psi. Compounds were identified based on their mass spectral data.

2.6.2. HPLC analysis. Analysis of phenolic compounds was carried out in Tehran Unversity, Iran using A waters liquid chromatography apparatus consisting of a Separations module: waters 2695 (USA) and a PDA Detector waters 996 (USA). Data acquisition and integration were performed with Millennium 32 software. The injection was an autosampler injector equipped with the chromatographic. The assay was performed on a 15 cm×4.6 mm with pre-column, Eurospher 100-5 C18 analytical column provided by waters (Sunfire) reversed-phase matrix (3.5 µm) (Waters). And elution was carried out in a gradient system with methanol as the organic phase (solvent A) and distilled water (solvent B). The gradient programme was as follows: 15%A/85%B 0–12 min, 40%A/60%B 12–14 min, 60%A/40%B 14–18 min, 80%A/20%B 18–20 min, 90%A/10%B 20–24 min, 100%A 24–28 min [33]. The flow-rate was kept at 1 mL min^{-1}. Peaks were monitored at 280 nm wavelength. The injection volume was 20 µL, and the temperature was maintained at 25°C. Phenolic compounds were identified according to their retention times and their peaks' spectral characteristics against those of standards.

2.7. Preparation of copolymeric hydrogels U1-U3

Copolymeric hydrogel U1 loaded with *Coriandrum Sativum* L. extract salt was prepared by dissolving 2 gm acryl amide and 0.2 gm of the cross-linked agent (N, N\-methylene bisacrylamide) in 5 mL of distilled water with stirring. Then, 1 mL of *Coriandrum Sativum* L. extract salt (0.05 mg/mL) was added. 2 g of 2-Acrylamido-2-methylpropane sulfonic acid (AMPS) was dissolved in 5 mL of water and added to the acryl amide solution with constant stirring at 30-35°C. Then 1 mL ammonium persulfate (10% W/V) was added as an initiator of the polymerization reaction and then add 5 drops of N,N,N\,N\tetramethylenediamine (TMEDA) as an accelerating agent for initiator dissociation with good mixing for three minutes until the polymerization, and crosslinking process is complete. The gel was cut off and left to dry at laboratory temperature. See Scheme 1.



Scheme 1. The reaction of preparing the copolymeric hydrogels (U1-U3).

The U2 and U3 hydrogels were prepared at the same protocol with different monomers ratio, as shown in table 2.

Table 2. Composition of materials for the preparation of hydrogels U1-U3.

Hydrogels	AcAm (g)	Bis AcAm (g)	AMPS (g)	Extract salt (mL)	Total polymer weight (g)	Ratio AMPS:AcAm
U1	3	1.2	3	1	7.2	1:1
U2	6	1.8	3	1	10.8	1:2
U3	3	1.8	6	1	10.8	2:1

2.8. Preparation of Simulated Gastric Fluid (SGF) and Simulated Intestine Fluid (SIF)
The Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) were prepared. According to the American Medicines Encyclopedia [34].

2.9. Scanning electron microscope (SEM) of (U1-U3) hydrogels
The prepared copolymeric hydrogels (U1-U3) were dipped in distilled water. After reaching the equilibrium swelling ratio, the hydrogels were removed from the distilled water, freezing and carried out under freeze-drying for 3 hours at (-48°C) to preserve their porous structure. Then, they are examined using a scanning electron microscope SEM.

2.10. Swelling and release studies of prepared hydrogels
The swelling ratio and release rate of the copolymeric hydrogels was studied in different pH at 37°C. The copolymeric hydrogels species were immersed in distilled water (pH=6.9), SGF (pH=2.1) and SIF (pH=8.2) solutions and at different time intervals. The swelling ratio was calculated according to the following equation [35].

$$Swelling\ ratio = \frac{Ws-Wd}{Wd} * 100\%$$

Where Wd= dry weight of hydrogel and Ws = the weight of the swollen hydrogels. The release of the phenolic extract was followed using a UV-vis spectrophotometer with time intervals.

2.11. Set standard calibration curves for Coriandrum Sativum L. extract salt
The λ_{max} of the *Coriandrum Stavium* L. extract salt was determined using ultraviolet spectroscopy, where the extracted salt showed absorbance at the wavelength (636 nm) in distilled water. Simulated Gastric and Intestine Fluids showed absorbance at the wavelength (655 nm), (665 nm), respectively.

2.12. DPPH radical scavenging activity of phenolic extracts 4, 8, and the extracts released from the polymers
The obtained extracts electron donation ability was tested by bleaching the purple-coloured solution of 1,1-diphenyl-2 picrylhydrazyl radical (DPPH) in line with the method [36]. One mL different concentrations of extracts (1, 10, 100 and 200 μg/mL) prepared in ethanol were added to 1 mL of a 0.2 mmol/L DPPH ethanolic solution. The mixture was shaken vigorously and left standing at room temperature for 30 min. The absorbance of the resulting solution was then measured at 517 nm after 30 min. The antiradical was expressed as IC_{50} (mg/mL), the concentration required to cause a 50% DPPH inhibition. The ability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH scavenging effect (\%)} = \{[A_0 - A_1] / A_0\} \times 100$$

A_0 is the absorbance of the control at 30 min, and A_1 is the absorbance of the sample at 30 min. BHT was used as a positive control.

2.13. Statistical analysis

Phenolic extracts were assays in duplicate, and results were expressed based on dry matter weight. Data are expressed as mean ± SD. The means were compared using the one-way and multivariate analysis of variance (ANOVA). The differences between individual means were deemed to be significant at $p < 0.05$. All analyses were performed by using the "Minitab 19" software.

3. Results and discussion

3.1. Total phenolic, total flavonoid and total tannin contents

Total phenolic contents in methanolic and ethanolic extracts of *Coriandrum Sativum* L. is shown in table 3. Total phenolic content expressed as mg gallic acid equivalent per gram dry weight. The extracts exhibited high phenol content with 9.822, 9.364 and 8.373 mg GAE/g DW in extract 7, 4 and 3, respectively. Thus, the order of the total phenolic content of all extracts determined by the Folin -Ciocalteu method is as follows: (L) ethanolic extracts > (L+S) ethanolic extracts > methanolic extracts for both (L) and (L+S).

Table 3. Total phenolic, flavonoid and tannin contents of *Coriandrum Sativum* L. parts.

No. of extracts	Type of Extracts	Total phenol content mg GAE/g DW	Total flavonoids content mg QE/g DW	Total tannin content mg QE/g DW
1	(L+S) in methanol at 30 min	5.921 ± 0.361	4.472 ± 0.121	2.650 ± 0.070
2	(L+S) in methanol at 24 h	4.689 ± 0.187	3.793 ± 0.928	4.245 ± 0.276
3	(L+S) in ethanol at 30 min	8.373 ± 0.168	3.422 ± 0.044	1.935 ± 0.077
4	(L+S) in ethanol at 24 h	9.364 ± 0.012	7.909 ± 0.160	1.840 ± 0.141
5	(L) in methanol at 30 min	7.308 ± 0.218	5.213 ± 0.186	1.480 ± 0.070
6	(L) in methanol at 24 h	4.015 ± 0.118	2.811 ± 0.371	1.135 ± 0.091
7	(L) in ethanol at 30 min	9.822 ± 0.634	7.957 ± 0.014	1.855 ± 0.077
8	(L) in ethanol at 24 h	7.726 ± 0.124	8.112 ± 0.115	1.855 ± 0.106

Values are duplicate ± standard deviation; data were compared statistically by one-way ANOVA at $p = 0.000$

In India, Jangra *et al*. analyzed the total phenols found in the ethanolic extract of *Coriandrum Sativum* L. leave ranged from 6.14-7.27 mg GAE/g DW of total phenol. And this is close to our results, while the extract with acetone and water was ranged from 5.06-6.18 mg GAE/g DW, 6.97-8.97) mg GAE/g DW respectively [37]. The other work demonstrated that the ethanolic extract of *Coriandrum Sativum* L. leaves 0.36 mg GAE/g DW of total phenol [38] and this is less than our present study. On the other hand, a study from Udaipur (Agrawal *et al*. 2016) found that the extraction solvents significantly affected the extract's polyphenol content. Flavonoids are one of the phenolic compounds that widely spread in leaves, seeds, bark,

and plant flowers, and they are responsible for the colours of plants and the blue and red colours of berries and wines [39]. Quercetin dihydrate was taken as standard flavonoid, and results were represented as mg quercetin equivalent per gram dry weight (mg QE/g DW).

The flavonoid contents varied according to the fractions of *Coriandrum Sativum* L.and the solvent used. Extract 8 showed maximum flavonoids content of 8.112 mg QE/g DW, followed by extract 7 and 4 with mean value 7.957 and7.909 QE/g DW respectively, as shown in table 3. Ethanolic extract shows higher TFC than methanolic extracts. The leaves (L) extracts in ethanol and methanol showed more flavonoids substances than leaves and stems mixture (L+S) extracts. Jangra SS, Madan V, Singh I Analyzed the total flavonoids in India's study; they found in the ethanolic extract of *Coriandrum Sativum* L. leaves ranged from 8.35-9.41 mg QE/g DW [37]. These results were close to the present study results.

Total tannin content expressed as mg Quercetin equivalent per gram dry weight. In general, the leaves and stems mixture (L+S) extracts in ethanol and methanol showed more tannins substances than the leaves extracts (L). extract 2 showed maximum tannin content of 4.245 mg QE/g DW. There are no previous studies to estimate tannins in *Coriandrum Sativum* L. leaves and stems mixture or leaves.

3.2. Phenolic identification by HPLC and GC-MS

The results of GC-MS revealed that the (L+S) and (L) of *Coriandrum Sativum* L. have one phenolic compounds *O*-tert-Butyl-*p*-cresol contributing to about 21.27% in (L+S) and approximately 16.47% in (L). See Figure 1.

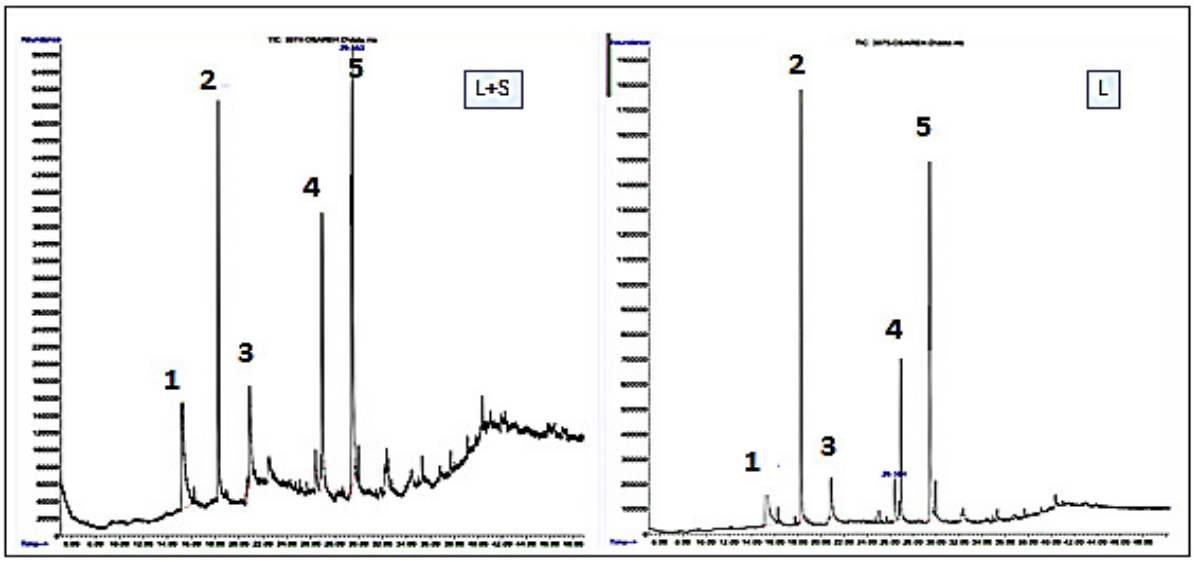


Figure 1. Gas chromatography and mass spectroscopy (GC-MS) for (L+S) and (L) dried samples Peaks numbers corresponding to: 1. *O*-tert-Butyl-*p*-cresol, 2. Butylated hydroxytoluene, 3. Citroflex 2, 4. Palmitic acid, ethyl ester, 5. Linolenic acid, ethyl ester. Peaks without numbers were not identified.

In addition, non-phenolic compounds in the *Coriandrum Sativum* L. were identified by comparing their mass spectra with the database of the spectrum of known components stored in the Gas Chromatography-Mass Spectrometry library, as shown in table 4.

Table 4. Phytocomponents identified for (L+S) and (L) dried samples of *Coriandrum Sativum* L. using GC-MS.

PK. No.	RT (min)	Area%		Name of compound
		(L+S)	**(L)**	
1	15.251	21.27	16.47	*O-tert*-Butyl-*p*-cresol
2	18.261	15.78	22.16	Butylated hydroxytoluene (BHT)
3	20.871	10.81	5.19	Citroflex 2
4	26.936	14.83	11.66	Palmitic acid, ethyl ester
5	29.453	37.30	40.28	Linolenic acid, ethyl ester

On the other hands, HPLC (L+S) and (L) dried samples revealed the presence of three phenolic compounds in both samples (L+S) and (L) as shown in figure 2.

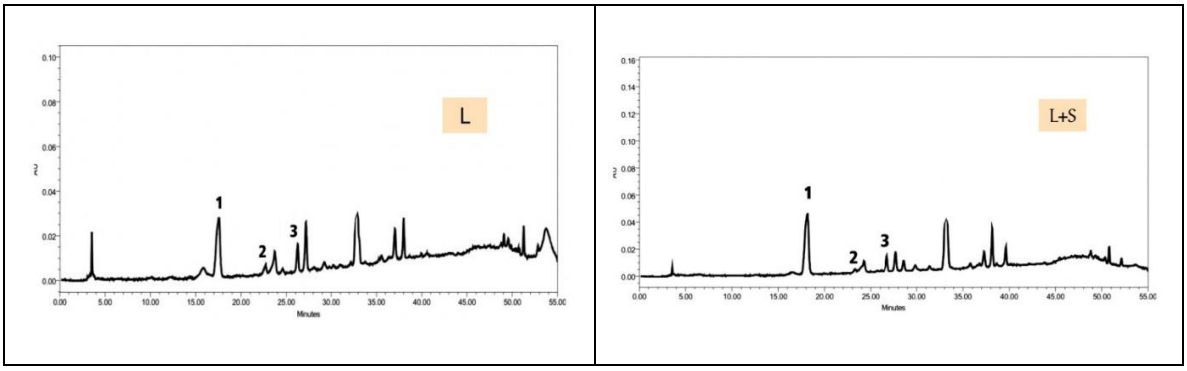


Figure 2. HPLC chromatogram of Coriandrum Sativum L. (L+S) and (L), the signal was collected at λ 195-400 nm. Peaks numbers corresponding to 1. Caffeic acid, 2. *p*-coumaric acid, 3. Chicoric acid. Peaks without numbers were not identified.

Table 5. HPLC chromatogram of Phenolic compounds present in *Coriandrum Sativum L.* (L+S) and (L).

PK.No.	Peak name	Retention Time (Min)		µg/5mg DW		Area [%]	
		(L+S)	(L)	(L+S)	(L)	(L+S)	(L)
1	Caffeic acid	18.150	17.555	16.99	10.59	86.01	75.23
2	*p*-coumaric acid	23.309	22.690	0.2	0.08	4.77	5.86
3	Chicoric acid	26.752	26.256	3.05	4.16	9.20	18.90

Caffeic acid contributing for about 86.016% (16.99 mg/100 g DW) in (L+S) and about 75.232% (10.59 mg/100 g DW) in (L). *P*–coumaric acid (4.779%, 0.2 mg/100 g DW) in (L+S) and (5.863%, 0.08mg/100 g DW) in (L), and chicoric acid (9.203%, 3.05mg/100 g DW) in (L+S) and about (18.903%, 4.16 mg/100 g

DW) in (L) were identified by comparison of their retention times with authentic standards analyzed under the same conditions, as shown in table 5.

3.3. Morphology of the prepared hydrogels

The copolymeric hydrogels were analysis by scanning electron microscopy. Figure 3 of prepared copolymeric hydrogels (U1-U3) find that an unregular shape with many holes results from their swelling. As the number of acrylamide decreases, the pore size decreases when compared between U1 and U3. The surface roughness becomes less in the case of U3 hydrogel due to the small pore size. Therefore, the U1 hydrogel gave a higher swelling ratio than the U3 hydrogel. SEM image of the U2 hydrogel in a shrinking state shows that the shrinking gel does not have any pores, so the surface appears regular and smooth except for some small bumps in nano size.

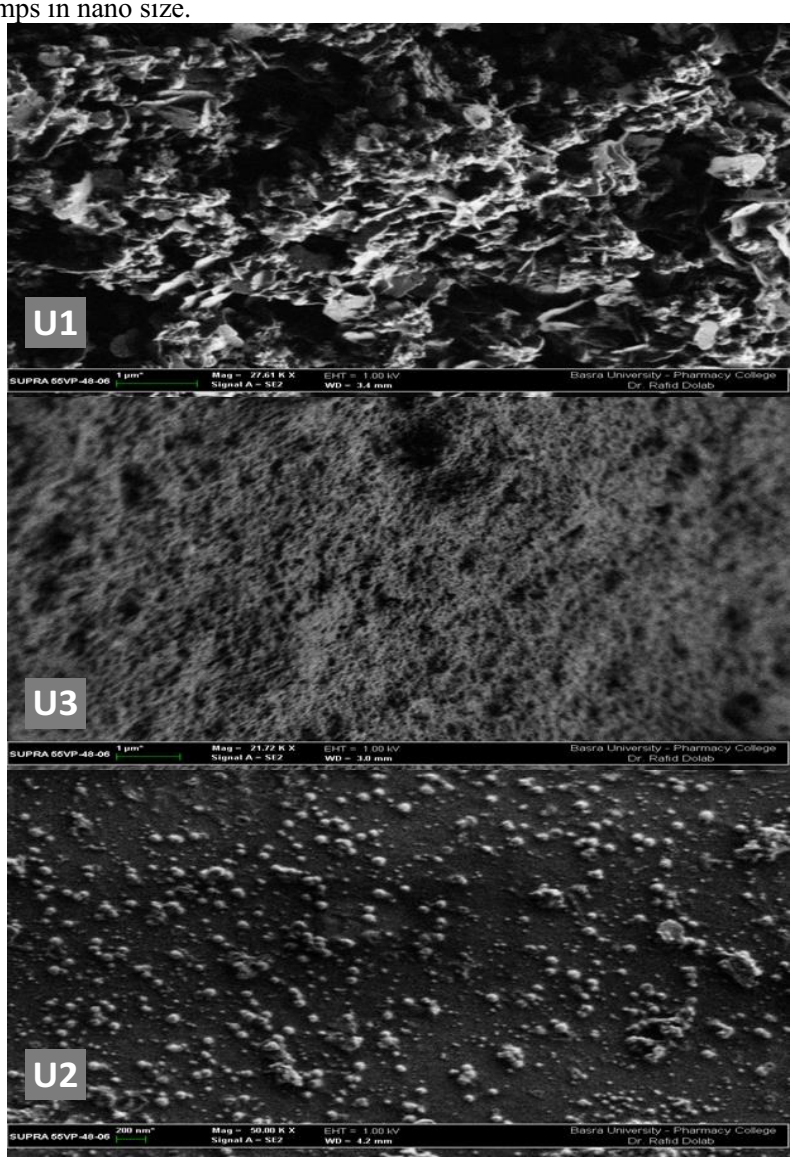
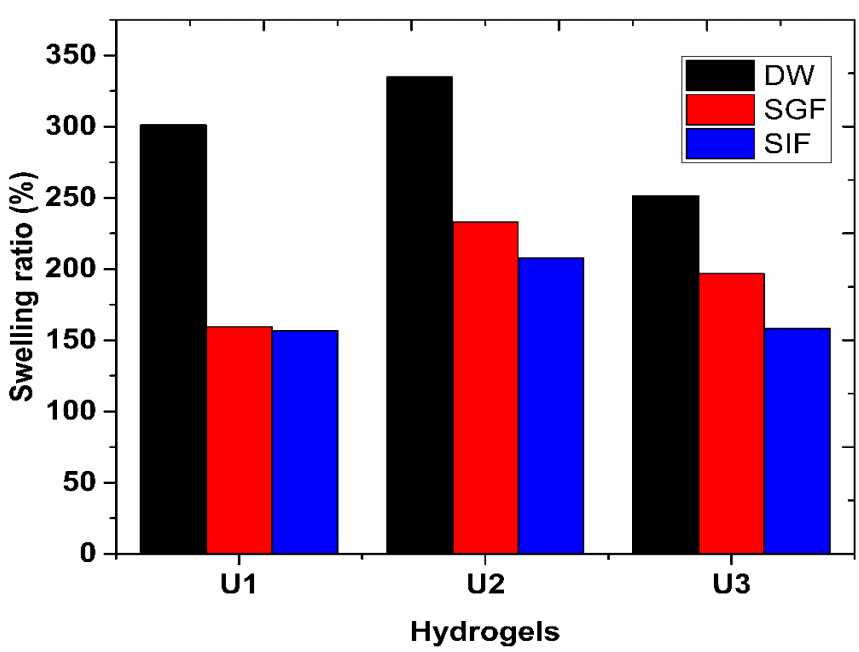


Figure 3. SEM images of U1, U3 in a swell state and U3 in a shrinking state.

3.4. Bioapplications of Iraqi Coriandrum Sativum L. extracts and the copolymeric hydrogels loaded with extract salt

3.4.1. drug delivery system. The swelling ratio of the prepared copolymeric hydrogels was determined as a function of time in distilled water, SFG and SIF at 37°C and six hours. The pH of the swelling medium is one of the crucial factors affecting a hydrogel's swelling behaviour [40]. Scheme 2 shows the results of the swelling ratios of copolymeric hydrogels U1-U3.



Scheme 2. **The swelling ratio for hydrogels (U1-U3) at SIF, SGF and distilled water**

The maximum swelling of copolymeric hydrogel was observed at pH 6.9 (in distilled water) due to ionization of $–SO_3H$ groups in AMPS. These sulfonate groups can be ionized quite easily, even in neutral pH, and it allures the polar water molecules to enter into the crosslinked network. The cage structure has been formed from the intermolecular H-bonding between the amide's carbonyl group and the AMPS unit acid moieties. It may lead to designs that can hold many water molecules [41]. Also, the presence of hydrophilic groups ($CONH_2$ secondary amine) that are present in the copolymeric hydrogels (AcAm-co-AMPS) have an impact on the swelling behavior [42], as the amide group enhances the hydrogen bonding between copolymeric structures and water molecules [43].

In an acidic medium (SGF, pH<7), the amino groups may protonate. Thus, the acidic protons of sulfonyl groups of AMPS interact with the amide group's nitrogen or oxygen from acrylamide, which prevents polymer water interaction. And the formation of the desirable H-bond responsible for accommodating water molecules and thus may be responsible for reducing equilibrium swelling [44, 45]. An increase in protonation amide groups will generate electrostatic repulsion between neighbouring ions in the hydrogel's polymer structure and the ions in the hypothetical gastric solution quaternary ammonium groups responsible for polymer swelling [46].

In a simulated intestinal fluid (pH=8.2), the acidic group's ionisation increases due to the deprotonation process. Many SO_3^- ions are formed, which repel each other, leading to the cage structure's disturbance and

reduce swelling [41]. On further increases in AMPS content (beyond 10 mol%), the content of the strong ionic group-SO_3H will increase in the polymer network. Thus, maybe expected to create ionic repulsion between the similar charges leads to the increased distance between the functional groups, resulting in a gradual decrease in hydrogen bonds forming, which prevents the water molecule penetration inside the network [44]. Thus the swelling decreases gradually with an increasing amount of AMPS. While increasing the amount of AM, the hydrogels' swelling ratios are found to grow.

The released percentage of phenolic extract salt with time was studied at room temperature (37°C) in distilled water, SGF and SIF for nine hours. Figure 4 shows there are no significant differences in the rate of phenolic extract salt in SGF solution. So, there is no effect of the acidic medium on the release rate of phenolic extract from the copolymeric hydrogel.

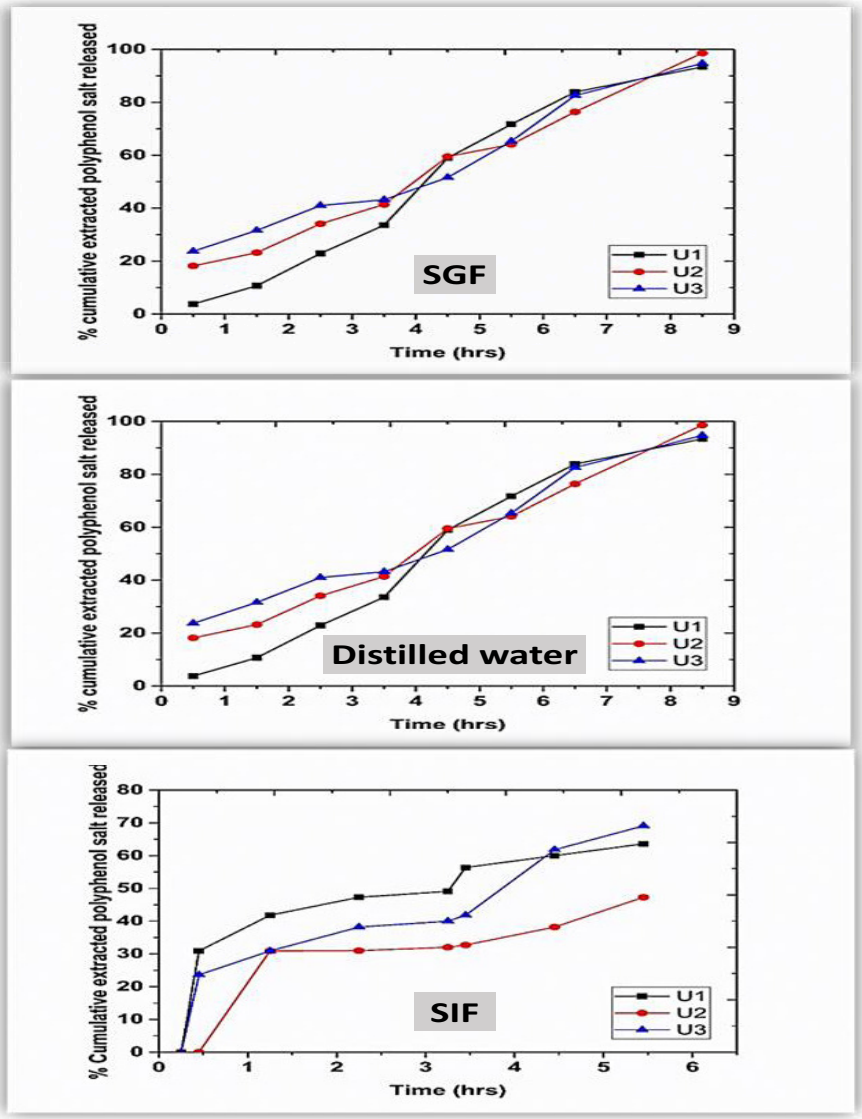


Figure 4. The release percentage of cumulative extracted phenol extract salt from copolymeric hydrogels U1-U3 in SGF, distilled water, and SIF.

Figure 4 indicates that by increasing the amount of acryl amide in the gel structure (U2), the phenolic extract's release rate is high distilled water. That maybe due to the high swelling ratio of the hydrogel U2 in distilled water compared to the other two hydrogels U1 and U3. Polyacrylamide has a very high swelling rate when immersed in water [47]. It leads to the formation of large pore size quickly, which explains that the highest release rate of phenolic extract salt from the hydrogel U1 compares with U3, which has the least amount of polyacrylamide.

The hydrogel U3 has a higher amount of AMPS. Thus, the possibility of forming hydrogen bonds between the gel and the phenolic extract salt will remain high due to the presence of non-ionized sulfonic acid groups and amine groups, so the rate of phenolic extract salt release decreases dramatically from within the hydrogel.

On the contrary, there are no noticeable differences in the release rate of phenolic extract salt from the U1 and U3 copolymeric hydrogels in the basic medium (SIF). Simultaneously, the U2 gel gives the lowest percentage of phenolic extract salt release because the sulfonic groups are completely ionized in the basic medium, which reduces the hydrogen bonds between the gel and the phenolic extract salt. Due to a more significant amount of acrylamide in the U2 hydrogel, maintaining the hydrogen bonds between the phenols and carbonyl groups remains possible.

Thus, the drug release depends on the composition of the hydrogel polymer and the active materials with hydrogels via physical interactions, the swelling ratio, and the pH of the environment [48].

The Higuchi release equation is the simplest mathematical equations. It was used to theoretically determine the percentage of released phenol extract salts as a function of time-based on the practical results obtained from a slow release of phenolic extract salt from all prepared copolymeric hydrogels in distilled water, SGF and SIF. Higuchi equation can be represented in the form:

$$Q_{(t)}=K_H \times t^{1/2}$$

$Q_{(t)}$ is the cumulative percentage phenol release, and K_H is the Higuchi dissolution constant [49]**.**

Hence, if the correlation coefficient (R^2) is high for this plot, the release mechanism follows a diffusion control release mechanism [50, 51]. See table 6. Thus, the Higuchi model confirmed the release mechanism.

Table 6. Higuchi dissolution constant and correlation coefficient (R^2) for released phenolic extract salts from copolymeric hydrogel (U1-U3) in distilled water, SGF and SIF.

Hydrogel	Distilled Water		SGF		SIF	
	K_H	R^2	K_H	R^2	K_H	R^2
U1	68.816	0.9895	48.872	0.9530	19.825	0.9553
U2	32.189	0.9919	44.511	0.8799	27.776	0.9952
U3	46.534	0.9444	44.189	0.9750	35.283	0.9410

*3.4.2. Antioxidant activity***.** Total antioxidant capacities of different parts of *Coriandrum Sativum* L. were significantly various. See table 7. The assay is based on reducing purple DPPH to a yellow-coloured diphenyl picrylhydrazine and the remaining DPPH. This ability was higher in extract 4 (77.46 mg GAE/g DW) and lowered in extract 8 (61.41 mg GAE/g DW). However, the DPPH scavenging abilities of the ethanolic extracts (L+S) and (L) were lower than those of synthetic antioxidant BHT.

Table 7. DPPH Radical Scavenging % at different concentration of *Coriandrum Sativum* L. phenolic extracts.

Phenolic extracts	DPPH Radical Scavenging % at Different Concentration of *C. Sativum* L. ethanol Extracts and BHT					IC_{50} µg/mL
	25 µg/mL	50 µg/mL	100 µg/mL	200 µg/mL	300 µg/mL	
Extract 4 (L+S)	16.3%	28%	36%	40%	59%	241.585 ± 0.007
Extract 8 (L)	3.2%	5%	14.2%	23.3%	32.4%	455.150 ± 0.071
BHT	38%	47%	59%	61%	65%	88.115 ± 0.163

Values are duplicate ± standard deviation; data were compared statistically by one-way ANOVA at p = 0.000

The high free radical scavenging activity of extract 4 is directly related to its high phenolic and flavonoid content (9.364 mg GAE/g DW) and (7.909 mg QE/g DW) where such a relationship has also been noted in other studies [9, 52].

There are no reports on the antioxidant capacities of *Coriandrum Sativum* L. for the composition of phenolic fraction present in the leaves and stems (L+S) and leaves (L) cultivated in Iraq.

The DPPH assay results for phenolic extracts released from the polymers (U1-U3) in distilled water, SGF, and SIF were presented in table 8.

Table 8. DPPH radical scavenging % activity for the phenolic extracts released from the copolymeric hydrogels.

sample	DPPH Radical Scavenging % of samples		
	in SGF	in SIF	in distilled water
Phenolic extracts released from U1	11.515 ± 0.276 at 88 µg/mL	17.1450 ± 0.0778 at 93 µg/mL	17.3150 ± 0.0212 at 93 µg/mL
Phenolic extracts released from U2	24.455 ± 0.488 at 100 µg/mL	8.3650 ± 0.0636 at 84 µg/mL	12.3900 ± 0.0141 at 88 µg/mL
Phenolic extracts released from U3	10.300 ± 0.283 at 85 µg/mL	14.5550 ± 0.0636 at 90 µg/mL	12.9050 ± 0.0212 at 88 µg/mL

Values are duplicate ± standard deviation; data were compared statistically by one-way ANOVA at p = 0.000

The scavenging activity on DPPH radicals for copolymeric hydrogels (U1-U3) ranged from 10.300 - 24.455% in SGF, from 8.3650-17.1450% in SIF, and from 12.3900-17.3150% in distilled water. These results are consistent with the results we obtained from the release study as the active extract is released from the copolymeric hydrogels. Thus, their radical scavenging activity increases.

4. Conclusion

The extraction methods play an essential role in extracting phenolic compounds, as it notices that different extraction methods give different in, yield, phenol, flavonoid, and tannin were obtained. The phytochemical, HPLC, and GC-MS analysis results showed phenolic compounds in Iraqi *Coriandrum Sativum* L. extracts. Hence, this enhances being a cure for many diseases. Ethanolic extracts of (L+S) and (L) showed more phenols and flavonoids content than methanolic extracts for both (L) and (L+S). Leaves and stems mixture (L+S) extracts in ethanol and methanol showed more tannins substances than the leaves extracts (L). SEM images of the prepared copolymeric hydrogels showed large pores that increased the speed of drug release. As AM increases, the hydrogels' swelling rates increase due to the hydrogen bonds between polymeric structures and water molecules. The ethanolic extract 4 (L+S) showed higher scavenging activity on DPPH radicals than extract 8 (L). The high free radical scavenging activity of extract 4 is directly related to its high phenolic and flavonoid content. Also, the study showed the scavenging activity of extracts released from the prepared copolymeric hydrogels.

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