Novel extraction, rapid assessment and bioavailability improvement of quercetin: A review

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ABSTRACT

Quercetin (QUR) have got the attention of scientific society frequently due to their wide range of potential applications. QUR has been the focal point for research in various fields, especially in food development. But, the QUR is highly unstable and can be interrupted by using conventional assessment methods. Therefore, researchers are focusing on novel extraction and non-invasive tools for the non-destructive assessment of QUR. The current review elaborates the different novel extraction (ultrasound-assisted extraction, microwave-assisted extraction, supercritical fluid extraction, and enzyme-assisted extraction) and non-destructive assessment techniques (fluorescence spectroscopy, terahertz spectroscopy, near-infrared spectroscopy, hyperspectral imaging, Raman spectroscopy, and surface-enhanced Raman spectroscopy) for the extraction and identification of QUR in agricultural products. The novel extraction approaches facilitate shorter extraction time, involve less organic solvent, and are environmentally friendly. While the non-destructive techniques are non-interruptive, label-free, reliable, accurate, and environmental friendly. The non-invasive spectroscopic and imaging methods are suitable for the sensitive detection of bioactive compounds than conventional techniques. QUR has potential therapeutic properties such as anti-obesity, anti-diabetes, antiallergic, antineoplastic agent, neuroprotector, antimicrobial, and antioxidant activities. Besides, due to the low bioavailability of QUR innovative drug delivery strategies (QUR loaded gel, QUR polymeric micelle, QUR nanoparticles, glucan-QUR conjugate, and QUR loaded mucoadhesive nanoemulsions) have been proposed to improve its bioavailability and providing novel therapeutic approaches.

1. Introduction

QUR (3, 5, 7, 3’, 4’-pentahydroxyflavone) is a dietary flavonoid, chemically comprised of three benzene rings and five hydroxyl groups, and abundantly present in flowers, stems, wine, tea, vegetables, bark roots, and vegetables (Table 1). QUR is a crystalline, yellow solid with a bitter taste, water-insoluble, and is an aglucone or aglycon which does not include any carbohydrate molecule in its structure and it imparts beautiful colors to a variety of flowers [1]. Furthermore, various studies have proved QURs potent therapeutic potential due to their anti-inflammatory [2], antineoplastic [3], antioxidant [4], neuroprotective [2], antiallergic [5], and antimicrobial activities [6]. Due to these health-promoting attributes, QUR obtained extensive approval and application in the pharmaceutical industry. The antineoplastic consequences of QUR are achieved by the alteration of WNT1/β-catenin and PI3K/Akt/mTOR pathways to assist cell apoptosis [7]. Researchers have also established that QUR can overcome the extreme expression of inflammatory cytokines [8]. Hence, the flavonoid is deemed an encouraging competitor to be employed as a powerful pharmaceutical tool for illness suppressions (Table 1). Furthermore, it also has satisfactory therapeutic potential to act as anti-obesity [9], anti-diabetes [10], and to relieve Alzheimer’s disease [11]. However, QURs comparatively lower bioavailability due to their low aqueous solubility, high metabolic rate, inactive metabolic products and rapid clearance.

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from body. Consequently, comprehensive attempts have been executed to reduce the toxicity and improve the bioavailability of the phytochemical by QUR encapsulation techniques. Currently, encapsulating delivery systems include lipid-based carriers [12,13], polymer nanoparticles, inclusion complexes, micelles, and conjugated-based capsules has been investigated [1]. Exceptional progress in bioavailability-related fields ensures improved therapeutics effectiveness to obtain more clinical advantages from QUR.

Keeping in view the health advantages, several novel extractions and assessment techniques have been adopted for the extraction and identification of QUR in agricultural products. Moreover, acknowledging the current high demand for food safety and quality assurance, researchers have performed experiments into exploring non-destructive, fast, and convenient novel approaches. Also, some scholars exerted their effort for QUR extraction through some emerging extraction modalities such as ultrasound-assisted extraction (UAE) [14], microwave-assisted extraction (MWAE) [15], supercritical fluid extraction (SFE) [16], enzymes extraction (EE), and [17], ultrasound-microwave extraction (UMWE) [18]. Nonetheless, scientists have also recently developed innovative non-destructive tools for QUR estimations including fluorescence spectroscopy, terahertz spectroscopy, near-infrared spectroscopy, hyperspectral imaging, Raman spectroscopy, and surface-enhanced Raman spectroscopy [19,20].

In the last few years, some review articles have been published, among them, most of the papers focused only on different therapeutic properties, while some discussed the conventional extraction techniques for QUR from different agricultural products. However, so far no attempt has covered advances in novel extraction techniques for QUR, emerging non-invasive assessment, and no review has elaborated recent strategies for bioavailability enhancement for the phytochemical. Therefore, we tried to cover recent advances in the three aforementioned domains employed for QUR. The first part describes the novel extraction techniques for QUR, while the second section represents the applications of recent non-invasive methods for rapid assessment of the phytochemical and elaborates the strengths and weaknesses of the methods used in different studies. Furthermore, the last part highlights the bioavailability improvement approaches for QUR such as QUR loaded gel, QUR nanoparticles, QUR loaded polymeric micelle, glucan-QUR conjugate, and QUR loaded mucoadhesive nanoemulsions.

2. Novel techniques for the extraction of quercetin

Conventional extraction methods such as maceration, soxhlet, hydro distillation, and heat-reflux extraction have been performed for decades for the extraction of flavonoids. However, the techniques need long treatment times, high temperatures, involve more solvents, only trained personnel can operate the equipment, environmentally unfriendly and the systems are cost-ineffective. Therefore, to overcome these drawbacks, some alternative novel extraction techniques have been developed and successfully adopted for the extraction of QUR (Table 2). These methods include ultrasound-assisted extraction (UAE), microwave-assisted extraction (MWAE), supercritical fluid extraction (SFE), and enzyme-assisted extraction (EAE). Each technique has a unique mechanism to enhance extraction and principles and processing parameters. The novel extraction approaches facilitate shorter extraction time, involve less organic solvent, and are environmentally friendly.

2.1. Ultrasound-assisted extraction (UAE)

UAE is an emerging extraction tool that requires a shorter reaction time, simple to operate, and minimum releasing of toxic solvents in the environment. During extraction ultrasound possibly increase the penetration of solvent, rupturing the cell walls and increase contact surface area, and encourages the soluble compound solvation [21–23]. In the UAE treatment temperature, time, power, and liquid–solid ratio affect the flavonoids extraction. In UAE, when the liquid–solid ratio is enhanced the extraction yield quickly improves. One limitation of the UAE is the decomposition of active ingredients by ultrasound waves. Jang, Asnin, Nile, Keum, Kim and Park [24] designed a method for QUR extraction from onion solid waste with an aqueous ethanol solution under ultrasonic treatment. The study concluded that ethanol concentration (40–80%, v/v) and extraction temperature (40–60°C) were the most important parameters affecting the recovery rate. While the pH, liquid/solid extraction ratio, and mining time had no significant effect on the integrity of the extraction. The best extraction yield of QUR (11.08 mg/g dry weight) was obtained with 59% ethanol with 49°C extraction temperature from onion dry waste. Similarly, another study was designed to compare various extraction methods for QUR from Raphanus sativus leaves. Results showed UAE as the best extraction approach for the flavonoid at 50% of ultrasound intensity for 10 min in methanol. Higher QUR content was detected with UAE as compared to

Table 1
Concentrations of QUR in some selected plant sources and their therapeutic properties.

| Common name         | Scientific name | Sources (mg/100 g) | Therapeutic properties                                                                 |
|---------------------|-----------------|--------------------|---------------------------------------------------------------------------------------|
| Raw Celery          | Apium graveolens| 3.51               | Lowers blood pressure, Lowers glucose, Anti-inflammatory, Antibacterial, Antihypertensive, Wound healing, |
| Raw Kale            | Brassica oleracea| 23.1              | Antioxidant, Reduce depressive disorders, Neurological effects, Reduce the risk of stroke, Neuropathy, Reduce cholesterol, Reduce dyspepsia, Antiinflammatory, Antiulcer, Anti-tussive, Iron deficiency anemia, Reduce osteoporosis, Anti-laxative, Antiviral, Antispasmodic, Antidiabetic, Disinfectants, Antiatherosclerotic agent, and Anti-cancer (1,2,4,5,82,159) |
| Raw Sweet           | Prunus armeniaca| 1.24               |                                                                                       |
| Welsh onion         | Allium fistulosum| 5.20              |                                                                                       |
| Red onion           | Allium capi     | 19.9               |                                                                                       |
| Black grapes        | Vitis vinifera  | 2.56               |                                                                                       |
| Broccoli            | Brassica oleracea| 3.10              |                                                                                       |
| Tomato              | Solanum        | 4.13               |                                                                                       |
| Coriander           | Coriandrum      | 5.01               |                                                                                       |
| Lettuce, raw        | Lactuca sativa  | 8.00               |                                                                                       |
| Raw                 | Nasturtium      | 30.0               |                                                                                       |
| Watercress          | officinalis     |                    |                                                                                       |
| Plums               | Prunus domestica| 2.00               |                                                                                       |
| Apple               | Malus domestica | 4.70               |                                                                                       |
| Cranberry           | Vaccinium       | 14.3               |                                                                                       |
| Okra                | Abelmoschus     | 21.0               |                                                                                       |

Sources of QUR references: Source: http://www.swisstargetprediction.ch, [1,82,159].
Novel extraction of QUR from agricultural products.

Table 2

| Technique | Matrix | Optimum conditions and extraction yield | References |
|-----------|--------|----------------------------------------|------------|
| UAE       | Euonymus alatus (Thunb.) Sieb | Aqueous ethanol 70%, extraction time 3 × 30 min, solvent: sample ratio 40:1 (v/v), and QUR extraction yield 0.29 mg/g | [160] |
|           | Raphanus sativus L. | Ultrasound intensity 50%, frequency 50/60 KHz, time 10 min, solvent methanol and QUR extraction yield 11.8% | [25] |
|           | Onion solid wastes | Ethanol 59%, temperature of 49°C, and total QUR yield 11.08 mg/g dry weight | [24] |
|           | Dendrobium officinale | Ethanol 90%, Temperature 50°C, Time 60 min, power 140 W, liquid ratio 60%, and QUR yield 4.3385 μg/g | [161] |
|           | Apple Peels | Treatment time 15 min of ultrasound wavelengths of dehydrated apple peel powder in 80% to 100% (v/v) methanol in 1:50 (w: v) solid to solvent ratio provided the optimum extraction conditions for quercetin | [31] |
|           | Onion skin | Treatment time 21.7 min, power 606.4 W with 43.8% ethanol and QUR yield 20.3% | [162] |
|           | Allamanda catharica | Total flavonoids yield was 172.90 mg QE/g and QUR yielded 51.39 mg/g | [163] |
|           | Abies nephrolepis (Trautv.) | Ultrasound power of 160 W, frequency of 45 kHz, the temperature of 332.19 K, extraction time 39.25 min, the ethanol concentration of 50%, a liquid-solid ratio of 20 mL/g, and QUR yielded 69.59 ± 2.57 mg/g | [27] |
|           | Cabbage | Sonication by 60:40 methanol/water (v/v), temperature 30°C, time 40 min, and QUR yielded 1378. 9 μg/mL | [164] |
|           | Hypericum perforatum L. | Extraction temperature 67°C, time 67 min, HCl concentration 1.2 M, methanol concentration 77% (v/v) and QUR yielded 10.81 mg/g | [165] |
|           | Ros populi | Temperature 70°C, liquid-solid ratio 25 mL/g, particle diameter 0.18 mm, ethanol concentration 60%, ultrasonic time 35 min, ultrasonic intensity 3.3 W/cm² and two experimental runs. Under these optimum conditions, approximately 16.26 mg of QUR was obtained from 1 g of Flos populi | [26] |
|           | MWA E | MW power 170 W, irradiation time 6 min, 50% ethanol (v/v) solution, extractant volume 40 mL | [166] |
|           | Solid Onion (Allium cepa L.) | MW irradiation for 150 sec at pH 6.25 yielded QUR 209 mg/100 gm fresh weight | [32] |
|           | Red Kidney Bean | Solvent 60 w/w% aceton, solvent to solid ratio was 10:1 and the MW irradiation power 800 W, treatment time 1 min and QUR yielded 35.8 mg/g | [167] |
|           | Carica papaya flower | Solid to liquid ratio (1:15), MW power 400 W, extraction time 4 min, and QUR yielded 0.214% | [33] |
|           | Lonicera edodes stem | MW radiation power 385 W, irradiation time 50 s, ethanol | [168] |

Table 2 (continued)

| Technique | Matrix | Optimum conditions and extraction yield | References |
|-----------|--------|----------------------------------------|------------|
| UMWA E Red onion skin wastes | MW irradiation time 60 s followed by sonication time 15 min at 70°C, 70% ethanol, solvent to solid ratio of 30 mL/g and yielded QUR 7.66% and total flavonoids 10.18% extraction yield | [169] |
| Iranian Propolis | MW power 300 W, irradiation time 1.5 min and ultrasound treatment time 10 min and temperature 40°C obtained QUR yield 44.53% | [170] |
| SFE | Sumac (Rhizomerae L.) | Temperature 40°C, pressure 250 bar, 6% ethanol content and yielded QUR 2196 μg/100 g | [171] |
|           | Onion skin | Extraction time 15 min, temperature 165°C, the mixture ratio of 1:5:2:5 for onion skin and diatomaceous earth and yielded QUR 16.29 ± 0.75 mg/g | [41] |
|           | Rosa damascena Mill | The temperature of 46.3°C, Pressure 25.5 MPa, CO₂ flow rate of 0.7 mL/min, extraction time of 120 min and yielded QUR 32.0% | [173] |
|           | Phyllanthus niruri Callus Culture | Temperature 60°C, pressure 200 bars, time 30 min and yielded QUR 1.72% | [174] |
|           | Taxus chinensis | Temperature 46°C, pressure 24 MPa, time 2.3 h, solvent 82% ethanol and yielded QUR 3.73 mg/g | [175] |
| EAE | Medicago Sativa L. | Enzymolysis time 92 min, ethanol concentration 22%, liquid/solid ratio was 40:1 (mL/g) and yielded QUR 12.56 μg/g | [46] |
|           | Onions | Ethanol concentration 5%, flow rate 3 mL/min, temperature 84°C, pH 5.5, and yielded maximum QUR | [47] |
|           | Onion peel waste | Pectinase 0.16 mg, cellulose 0.72 mg, xylanase 1.0 mg, and QUR yield was enhanced by 1.61 folds | |

Moreover, Wang, Goldsmith, Zhao, Zhao, Sheng and Yu [26] conducted a study to optimize the five types of flavonoids (QUR, luteolin, apigenin, pine cortex, and chrysanthemum) extracted from Schisandra. A combination of the Plackett-Burman design and the Taguchi method was used to adjust the process parameters of the UAE. Based on the single-factor investigation, the Plackett-Burman tool was originally adopted and revealed that temperature, particle size, ultra-sonication time, and intensity greatly affect the extraction rate. Moreover, the Taguchi method was useful for further assessment of the best conditions. The best outcomes (16.26 mg/g of sample) were obtained with the soxhlet, maceration, and digestion method Sharifi, Mahernia and Amanlou [25]. Additionally, Wang, Goldsmith, Zhao, Zhao, Sheng and Yu [26] studied the extraction behavior of three phytochemicals QUR, dioxim, and taxifolin from the leaves and bark of Abies nephrolepis. Kinetic harmony of extraction yield for 3 kinds of flavonoids was performed with a first-order kinetic model. From the thermodynamic analysis results, it was concluded that the UAE of the QUR, dioxim, and taxifolin from the samples leaves and bark is a spontaneous endothermic process in which the disorder is exacerbated. Also, Thuy, Tuyen, Cuong, Huyen, Phuong, Nguyen, Kim, Thu and Tai [14] carried out the extraction and
identification of QUR from the skin and flesh of shallot. A higher yield was obtained with the UAE than the solvent extraction technique. UAE improved the extraction yield of QUR by 13.38–15.64% for shallot skin and 49.46–56.88% for the flesh.

2.2. Microwave-assisted extraction (MWA)

MWA applies microwave energy to generate the rotation of dipole molecules. At the same time temperature of the solvent quickly rises, which breaks/ruptures the cell wall of the sample and stimulates the extraction of target compounds [23]. During MWA operation, the power of microwave irradiation is an important factor affecting the extraction yield, powerful irradiation increases the temperature of the extraction solvent and, sample matrix and improving the rate of mass transfer as well. The microwave irradiation time is also an important factor for extraction yield, as increasing time at a specific limit the extraction yield distinctly improves. For solvent, energy, and time-saving, 1 to 3 extraction cycles are sufficient to obtain a higher yield [28,29]. One limitation of MWA is the selection of solvent. Only those solvents are suitable which can absorb microwaves such as ethanol and methanol [29]. Earlier, a study was reported by Zhang, Yang, Su and Guo [30] for QUR and rutin investigations extracted from Eucommia ulmoides stalks using the MWA method. MWA results were compared with UAE and soxhlet extraction. The finding showed a higher extraction yield of 0.016 mg/g when compared with other approaches.

Similarly, three extraction methods (solvent extraction, UAE, and MWA) for QUR extraction from onion skin were also reported. The maximum extraction yield was 20.3–30.8 % obtained by MWA, higher than other extraction protocols Jin, Lim, oh Kim, Park, Jiang, Chung, Park, Shim and Choi [31]. Earlier, Kumar, Smita, Kumar, Cumbal and Alagusundaram [32] developed a facile renewable energy-based process to attain the optimum conditions for UAE and MWA. The effects of extraction time, pH, and other operating conditions for the QUR extraction rate were investigated. MWA ionic liquid-based silica adsorbents (ILs) were developed by using synthetic ionic liquids to chemically modify the surface of commercial silica. The resulting particles acted as a special adsorbent to separate QUR and its glycosides from the solid onion. As compared to traditional C18 adsorbents the ionic liquid-based silica adsorbent showed higher selectivity.

Recently, Mukhaimin, Saraswati, Ajizah and Triyastuti [33] also extracted QUR from dried flowers of Carica papaya through MWA with methanol (80%). Different microwave (MW) powers (120, 200, 280, and 400 W) and extraction time (1–5 min) were used in the study. The highest yield (0.214%) was obtained at 400 W MW power and 4 min of treatment time.

2.3. Ultrasound-microwave-assisted extraction (UMWA)

UMWA is another combination of novel techniques, used for the extraction of flavonoid compounds from plant sources [34]. During extraction, ultrasound possibly increases the penetration of solvents, rupturing the cell walls and increase contact surface area, and encouraging the soluble compound solvation [21,22]. Moreover, microwave improves the rate of mass transfer and solute solubility by rapidly increasing the sample temperature, and improving extraction efficiency by stimulating the desorption of the targeted compound’s action efficiency [29]. The irradiations of ultrasound and microwave simultaneously would add sufficient heat and energy to the extraction solvent, but it requires a specially designed system for the incorporation of both irradiations. Sun, Li, Ni, Yao, Jiang, Ren, Fu and Zhao [34] reported that the combination of microwave and ultrasound delivers high extraction yields and is valuable for heat-sensitive compounds.

A study was conducted by using the UMWA technique for the extraction of QUR from A. roxburghii powder. For effective extraction of QUR, ethanol concentration, extraction time, temperature, and liquid to solid ratio were regarded as important parameters. Temperature range of 50 °C, ethanol with 50% concentration, extraction time of 15 min, and the liquid–solid ratio of 8:1 delivered maximum QUR yield [35]. In another study, outcomes demonstrated that the UMWA is an effective tool for the extraction of QUR while high-speed counter-current chromatography was useful for QUR purification. This detachment strategy was more successful than some traditional procedures. The HSCCC test was performed with a two-phase solvent system made out of n-xylene, ethyl acetate derivation, methanol, and water (4:6:3:3, v/v/v/v). Every dissolvable blend was completely equilibrated in a separating funnel at room temperature [35].

2.4. Supercritical fluid extraction (SFE)

SFE is one of the separation methods developed in recent years. Supercritical fluid can be defined as any substance above its thermodynamic critical point which ultimately generates high diffusivity and low viscosity which helps to increase the transfer of matter [36]. Nowadays, SFE is widely employed not only in drugs and food but also in the fields of chemistry, toxicology, environment, petrochemical, textile, and polymers [37]. Notable executions of SFE in different research areas in the last three decades have promoted the extraction of bioactive compounds [38]. Chávez-González, Sepúlveda, Verma, Luna-García, Rodríguez-Durán, Iliana and Aguilar [39] reported that the SFE exhibited a higher extraction yield of flavonoids especially QUR.

Earlier, Léai, Martin, de Paz, Rodríguez-Rojto and Cocero [40] produced submicron encapsulated QUR particles by extracting biological solvents through SFE. Due to the speedy exclusion of organic solvent, the dispersed organic phase was rapidly oversaturated, causing submicron QUR particles to precipitate and become entangled with surfactant material. In an experiment using Pluronic, needle-shaped QUR atoms with a particle size of about 1 μm were obtained after SFE processing and the encapsulation efficiency was poor. For soybean lecithin, QUR loaded multivesicular liposomes with an average particle size of about 100 nm, the encapsulation efficiency of QUR up to 70% was obtained with no isolated QUR crystals.

Ghoreishi, Hedayati and Mousavi [41] carried out QUR extraction from Rosa damascena Mill by soxhlet extraction and modified SFE with ethanol. The pressure was adjusted from 10 to 30 MPa, extraction temperature was 35 to 55 °C, a flow rate of CO2 0.3 to 1.5 mL/min, and extraction time varied between 40 min and 2 h in the study. Response Surface Methodology (RSM) analysis confirmed that the modified R2 and R2 of the model were 87.1% and 93.1%, respectively. RSM test predicted the optimum operating temperature of 46.3 °C, the pressure of 25.5 MPa, extraction time of 2 h, and flow rate of CO2 0.7 mL/min, which showed the highest QUR yield of 32.0% in the study.

2.5. Enzyme-assisted extraction (EAE)

According to environmental laws and regulations concerning the extraction of a bioactive compound at an industrial scale, EAE is expected to attain broader popularity than conventional extraction techniques. Because conventional methods are acknowledged causes of environmental hazards due to their unusable residues, flammable solvents, and industrial methods needing a large number of steps [42]. Some recent studies on EAE have conferred faster extraction, higher recovery, less energy usage, and lower solvent consumption when collating with other methods. Moreover, EAE also offers numerous benefits such as using the whole plant material, mild reaction conditions, needing fewer steps for processing, extract the bioactive compounds with high quality and bioavailability [42,43]. The cell membrane micelles and cell wall structure are composed of macromolecules (polysaccharides and protein). So, during the extraction process, protein coagulation and denaturation are the principal barriers of extraction at high temperatures [44]. EAE improves the extraction yield and efficiency through enzymatic hydrolytic action on macromolecules, cell walls, and cell membranes inside the cell, which improves the
Strengths and weaknesses of non-destructive methods used in current work.

Table 3

| Techniques | Type       | Advantages                                                                 | Limitations                                                                                                       | References       |
|------------|------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------|
| FS         | Spectroscopic | Good signal–noise ratio, an abundant fluorophore                            | Autofluorescence, limited to the samples exhibiting fluoresce                                                      | [20,59,60,176,177] |
| THzS       | Spectroscopic | Use low energy and lower ionizing energy, Can generate frequency-domain and time-domain data from physical properties and chemical structure of the sample | Cannot penetrate in water and metals, scattering effect for irregular samples is also a weakness in THzS            |                  |
| NIRS       | Spectroscopic | The cost-effective tool can conduct qualitative and quantitative detections | Difficult to analyze samples containing water, can generate spectral data only                                       |                  |
| HIS imaging | Spectral imaging | provide spectral and spatial data, accurately differentiate the similar components of the sample even with similar color, can detect trace elements efficiently | Abundant redundant data, data processing needs a lot of time, adaptability of chemometric methods is another problem in HSI |                  |
| RS         | Spectroscopic | No interference to water, provide rich molecular Raman signatures          | Weak Raman scattering cost-ineffective                                                                            |                  |
| SERS       | Spectroscopic | An ultra-sensitive and specific tool, Direct/minor sample preparation needed, No interference to water and glass | Unstable hotspot regions in substrates, Sensitivity depends on the characteristics of employed nanoparticles         |                  |

Note: FS = fluorescence spectroscopy, THzS = terahertz spectroscopy, NIRS = near infrared spectroscopy, HSI = hyper spectral imaging, RS = Raman spectroscopy, SERS = surface enhanced Raman spectroscopy.

3.1. Fluorescence spectroscopy (FS)

FS is among fast spectroscopic methods that provide rapid spectral signatures (from samples) by estimating emission of light compares to absorbed UV or visible light. The samples absorb energy (from light) at a particular wavelength while releasing energy in form of emission with a higher wavelength [49]. However, the chemical, physical, and biological fluorescence spectra are typically overlapped. Moreover, the spectra seem very similar for different samples which make it difficult to differentiate the results. Thus chemometric models are needed to extract the target peaks from the overlapped data [50].

Owing to the non-destructiveness and rapidness attributes, FS has proved some promising results for QUR detection in different agricultural items (Table 4). For example, in a study, four medical plants were tested for quantification of QUR content using the FS method coupled with the partial least squares regression (PLSR) model. Among the tested samples R. himalense had the highest QUR values of 3.83% while, B. callioborysti exhibited 1.91%. A. eruetas showed 1.83% and S. muricatum delivered 0.87% respectively [51]. Similarly, emission spectra from Ziaphus murocanota and Ziaphus Sativa (medicinal plants) for QUR were determined using FS with the PLSR approach. Higher content of QUR was recorded from Z. murocanota samples as 1.50%. While Z. Sativa delivered 1.21% results for the tested parameter. Moreover, the Folin-Ciocalteu coloriometric assessment of samples also revealed former with higher QUR levels as compare to later [52]. Besides, Alabri, Hussain, Mabood, Rehman, Ali, Al-Harrasi, Hamaed, Khan, Biczvi and Jabeen [53] also ascertained QUR in Euphorbia mastrahensis plants with the FS-PLSR technique. The highest QUR content was determined from the samples with an n-butanol fraction (5.83%) with slope estimations of 0.997 and root mean square error (RMSE) of 0.355%.

3.2. Terahertz spectroscopy (THzS)

THzS is a fast spectral method with non-ionization features, extensively used for the discrimination of compounds with much similar molecular structures [54]. Terahertz is a small electromagnetic region between microwave (MW) and infrared (IR) spectrum, so the THzS generates an informative association between MW spectroscopy and IR spectroscopy. The noninvasive method works with frequencies ranging between 0.1 and 10 THz to determine torsional and rotational modes of vibrations from chemical compounds [19].

The rapid method was employed for the discrimination of three flavonoids (QUR, myricetin, and kaempferol) having similar structures.
Table 4 Nondestructive detection of QUR in agricultural products.

| Technique | Matrix | Model | Results | References |
|-----------|--------|-------|---------|------------|
| FS        | R. himalense, B. calliobaty, A. erentus, S. muricatum | PLSR | QUR yield in R. himalense = 3.83%, B. calliobaty = 1.91%, A. erentus = 1.83%, S. muricatum = 0.87% | [51] |
| THzS      | QUR, myricetin, and kaempferol | PLSR | QUR yield in Z. muricatum 1.50%, and Z. Sativa delivered 1.21% | [52] |
| NIRS      | Grapes and red wine | PLSR | Determined QUR (0.124% and 0.079%), TR, (0.447% and 0.124%), TPC (12.82% and 0.168%) and antioxidant % value (1.279% and 0.014%) for grapes and red wine samples | [55] |
| Mung bean (Vigna radiata L.) | PLSR | For quercetin, catechin, chlorogenic acid, caffeic acid, p-coumaric acid, t-furic acid, vittexin, isovitexin, myricetin, and kaempferol, R² more than 0.987 and RMSE-1.82% was recorded. For QUR: R² = 0.982, RMSEC = 1.771, R² = 0.969, RMSECV = 2.939 | [178] |
| Wine from DO Rías Baixas and DO Ribeira Sacra | PCR and PLS models | PLS showed good results as compare to PCR model. For DO Ribeira Sacra red wine: R²_ad = 0.82, RMSEC = 0.15, RMSECV = 0.55, RPD = 1.51. For wines from mencia grapes: R²_ad = 0.56, RMSEC = 0.24, RMSECV = 0.40, RPD = 1.12 | [179] |
| Grapes and grapes wine | PLS | Tested trans-resveratrol; QUR; gallic acid equivalent; Trolox equivalent in samples For QUR in grapes: SEC = 0.124, RPD = 0.973, SECV = 0.008, RPD = 0.977, RPD = 4.40 In wine: SEC = 0.078, RPD = 0.994, SECV = 0.073, RPD = 0.995, RPD = 9.0 | [61] |

Table 4 (continued)

| Technique | Matrix | Model | Results | References |
|-----------|--------|-------|---------|------------|
| HSI       | white grape marc | PLSR | QUR = 1.6 ± 0.1 mg/100 g dry mass, 2.1 ± 0.4 mg/100 g dry mass, and 2.0 ± 0.3 mg/100 g dry mass in the seed, skin, and stem of the samples. | [66] |
| RS        | dried onion | | R² = 0.9989 and 0.9998 for QUR in methanol and ethanol LOD = 5 x 10⁻⁶ mol/L | [75] |

TR = trans-resveratrol, TPC = total phenolic (TPC), R² = coefficient of determination, PLS: partial least squares regression, PLSR: partial least squares, LS-SVM: least-squares support vector machine, RMSE: root mean square error of prediction, RMSECV: root mean square error of cross-validation, RPD: residual predictive deviation, R²cv: coefficient of determination of cross-validation, R²cv, coefficient of determination for prediction.

3.3. Near-infrared spectroscopy (NIRS)

NIRS is another non-destructive spectroscopic approach, works best in spectra ranging from 780 to 2500 nm, detecting chemical bonds in a sample such as O-H, C-H, N-H, and S-H [56,57]. During an examination of a sample, the chemical bonds (in a sample) absorb spectral energy while, remaining NIR frequencies either reflect or transmit with the study. Results showed BTK with higher values for QUR, caffeine, and similar, the technique was also successfully applied for the evaluation of kombucha (k) prepared from black tea (BT) and green tea (GT) for bioactive compounds using a PCA chemometric model. QUR, chlorogenic acid, gallic acid, caffeine, catechin, and rutin were determined in the study. Results showed BTK with higher values for QUR, caffeine, and

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rutin as 1.22 mg/L, 177.37 mg/L, and 30.19 mg/L while, the GTK sample was dominant in chlorogenic acid (65.42 mg/L) respectively [62].

3.4. Hyperspectral imaging (HSI)

HSI is an optical sensing method that provides spatial and spectral information useful for the identification and quantifications of various components from a sample [59,63]. The rapid method is a combination of spectroscopy with digital imaging to produce a spatial map of spectral variations. A 3D ‘hypercube’ of image data (x, y, and λ) can be achieved by capturing a series of 2D spatial images as a function of wavelength and by superimposing the obtained data. HSI can be obtained as a 3D hypercube I (x, y, λ) or 2D spatial image I (x, y), or a combination of spectra I (λ) at pixel positions (x, y) [64,65]. However, the presence of many redundant data in hypercube needs extra computational work and time to extract target results, which limits HSI’s broader applications.

In addition to various food applications, HSI is also suitable for the assessment of phytochemicals in different food items. Recently, the tool was successfully applied to analyze 27 phenolic compounds from white grape marc (Vitis vinifera cv. Zalema) with the PLSR model. Among them, QUR was recorded to be 1.6 ± 0.1 mg/100 g dry mass, 2.1 ± 0.4 mg/100 g dry mass, and 2.0 ± 0.3 mg/100 g dry mass in the seed, skin, and stem of the samples. Also, the results for root mean square error of calibration (RMSEC) (0.16), R²C (0.79), root mean square error of cross-validation (RMSECV) (0.19), and R²CV (0.72) were also satisfactory, establishing that the proposed method was eco-friendly and non-destructive for the assessment of phenolic compounds in the sample [66].

3.5. Raman spectroscopy (RS) and surface-enhanced Raman spectroscopy (SERS)

RS is a versatile vibrational spectroscopic method that works on the inelastic Raman scattering principle. It provides Raman signatures for the quantification of various components in a sample [20,67]. The approach is preferred over other methods due to more sensitivity and specificity, direct analysis of a sample is possible, and has no interference to water in a sample. However, Raman scattering is a weak phenomenon, as only one photon out of one million photons follows the process [68]. Therefore, to enhance the weak Raman signals (in normal RS) researchers employed nanoparticles (NPs) near samples to enhance the peak intensities and the technique is called SERS [69]. By employing substrates, chemical and physical mechanisms can occur to boost the Raman signals. The chemical process occurs due to charge transfer between a sample and nano substrate while, amplification of signals due to optical attributes of NPs is a physical process [70,71]. The stable nanomaterial makes SERS an ultra-sensitive tool for numerous food and non-food detections. Gold, silver, and copper are simple and easily available NPs that are further employed for designing other sensitive SERS substrates [72-74].

Both RS and SERS have been extensively applied for different research areas in recent years [69]. The techniques are also suitable for the non-interruptive assessment of phytochemicals in agriculture items. For instance, RS equipped with an Argon ion laser having an excitation wavelength of 488 nm was employed for label-free detection of QUR in dried onion samples. Results revealed a high coefficient of determination (R²) of 0.9998 and 0.9998 for QUR in methanol and ethanol solvent with a limit of detection up to 5 x 10⁻⁵ mol/L [75]. Moreover, four different lasers with 532, 633, 785, and 1064 nm excitation wavelengths were used for the detection of QUR, flavone, 3-hydroxyflavone, and chrysin using RS and SERS method. With normal RS, the spectral intensity was greatly influenced for QUR and chrysin by different laser wavelengths, attributed to their high fluorescence resonance signals. Whereas, SERS based on AuNPs delivered good results for all the phytochemicals (even for QUR and chrysin), which depicted the sensitivity and quenching ability of SERS for high fluorescent materials [76]. The normal RS and SERS peaks for QUR using 532, 633, 785, and 1064 nm excitation wavelengths lasers are presented in Fig. 1. In another study, ethylenediamine-β-cyclodextrin (EIC) immobilized silver nanoparticles (AgNPs) embedded Silica (SiO₂) were used as SERS substrate for nondestructive detection of QUR, hesperetin, naringenin, and luteolin. The capturing ligand SiO₂ @Ag@Et-β-CDNPs improved the sensitivity down to 10⁻⁷ M for flavonoids detections [77].

4. Bioavailability enhancing strategies for QUR

Bioavailability is regarded as the specific amount of substance reaching the targeted site of action. Moreover, it is also an estimation of the dosage present as per the urinary measurement of its constituents and metabolites whereas, in the case of polyphenol absorption, bioavailability is considered as the amount present in plasma. In the pharmaceutical industry, ADME (absorption, metabolism, disposition, and excretion) is used as its comparable term [78-80]. In recent years, the characterization of quercetin (QUR) dosage and bioavailability from various agricultural products have been reviewed thoroughly by [81-85]. In the human body, QUR can only get ingested around 20 mg/day [86,87] while, the total plasma concentration of both free and conjugated QUR ranged from 72 to 193 nmol/L from QUR rich sources for short term intake. Whereas, long-term dietary usage does not result in plasma accumulation [88]. Due to the low solubility, it is also considered to have very low absorption in the gastrointestinal tract with oral bioavailability, calculated to be 1% in humans [89].

As per the biopharmaceutical classification system, QUR is classified in class IV with poor water solubility, low permeation, and a short biological half-life [90] (Fig. 2). Therefore, improvement in bioavailability is imperative for enhancing the application portfolio of the phytochemical [91]. Numerous delivery systems have been developed over the last decade to improve and modify the dispersed state of this bioactive constituent, which can enhance the chemical stability and increase the applications [92,93]. Current delivery systems include lipid-based carriers [94,95], polymer nanoparticles, inclusion complexes, micelles, and conjugated-based capsulations [88] (Table 5).

4.1. QUR loaded gel

To improve the solubilization and encapsulation properties of QUR, various formulations such as micro emulsions, microspheres, nanostructured lipid carriers, solid lipid nanoparticles, polymer nanoparticles are proposed. Whereas, the colloidal delivery system includes nanoemulsions (NE) ranging from 50 to 100 nm in size with a larger surface area, high drug loading capacity, sustained release, protection of drug candidates, and excellent permeation. But owing to the low viscosity NE, a gel system is also employed [96-99]. Such strategies improve the bioavailability of QUR and thus consequents in improved health maximum benefits. For example, administration of QUR incorporated with oleic: Arachis oil, tween 20, and PEG-400 (15:6:6) resulted in a successful carrier system with improved physicochemical stability, mechanical properties, skin permeability and exhibited good therapeutic effects for arthritis. The research concluded QUR-NE gel to have promising potential for complicated rheumatic disease [96].

In another research, NE prepared with QUR showed the highest solubility in cinnamon oil, followed by triacetin, castor oil, sesame oil, labrafac, palm oil, isopropyl myristate while, lowest in miglyitol. Experiments indicated that cinnamon oil, tween 80, carbitol @, poloxamer 407 with QUR improved the physical properties, gel stability, sol–gel transition, and syringe-ability. The administration among patients with periodontitis in in-vitro showed improvement in their condition [100].

In wound healing research, QUR loaded multiphase hydrogel was analyzed both in-vivo and in-vitro. The high entrapment efficiency of QUR and resveratrol was higher (92.85 & 89.85%) as compared to other liposomal nano-vector (71.20% QUR). These nano lipid carriers and
both QUR and resveratrol had potential in healing skin cancer with the latter two acting synergistically. Further, future research can also be focused on the cytotoxic impact on numerous cancer types with dermatokinetic studies [101]. Furthermore, in another research QUR-loaded liposomes in hydrogels improved gastric release up to 40% with significantly better texture, and the structure leading to lipogels cargo release enhancing the potential applications of the lipogels as a bio-food [102].

4.2. QUR nanoparticles (NPs)

Other than physical, chemical, and physiological properties including temperature, oxygen, and enzymatic activity of QUR, chemical instability and high biodegradability at different pH of the stomach has encouraged the researchers to preserve it in the hydrophobic matrices as NPs [103,104]. Among the natural polymer-based NPs, protein-based NPs are considered easy for the gastrointestinal tract [105]. QUR-NPs with bovine serum albumin (BSA) showed bioactivity in both the acidic and alkaline medium for longer durations [106]. Another study with QUR-loaded zein NPs by electro spraying was evaluated. The researcher determined in vitro gastrointestinal release of trapped QUR up to 79.1%, while, for free QUR it was 99.2%. The in vitro bioavailability was 5.9% for trapped while 1.9% for the free QUR, displaying better results with QUR zein NPs [103].

For polysaccharide-based NPs, QUR-loaded linoleic acid (LA) modified with chitosan oligosaccharis/β-lactoglobulin (CSO-LA/β-lg) NPs indicated higher cell permeation ability resulting in better quercetin accumulation in the skin (epidermis) [107]. Similarly, zein NPs were encapsulated with 2-hydroxypropyl-β-cyclodextrin with 300 nm diameter. The QUR release resulted in zero-order kinetic and oral bioavailability was calculated to be around 60% [108]. Moreover, improvement in solubility for QUR was also determined with the NPs prepared by using sodium alginate and chitosan polymeric microparticles through the ionic cross-linking approach [109,110].

Also, lipid-based Nanocarriers can resolve the bioavailability issues for QUR [111]. For instance, in vitro tests conducted to access bio-accessibility in simulated intestinal medium (SIM) was 60% in lipid nano-emulsions (LNEs), 50% in solid lipid NPs (SLNs), 40% in nano-structured lipid carriers (NLCs), and only 10% in the purest form. Similarly, another study evaluated the water solubility of QUR-loaded
### Table 5

| System                      | Process detail                                         | Therapeutic effect               | References |
|-----------------------------|--------------------------------------------------------|----------------------------------|------------|
| Hydrogels                   | Chemical: Hydrogels WPI QUR-LRA                         | Increase drug loading and release | [180]      |
|                             | Size (d): 179.5 nm                                       |                                  |            |
|                             | Entrapment capability: 92 %                             |                                  |            |
| Metal and metal oxide       | Chemical: Gold nanoparticles                             | Reduce the toxicity and activity | [181,182]  |
| nanoparticles               | Size (d): 100 nm                                        |                                  |            |
|                             | Entrapment capability: 79 %                             |                                  |            |
| Chitosan nanoparticle       | Chemical: QUR-chitosan conjugate-loaded with paclitaxel | Advanced aqueous solubility of novel anticancer | [183,184]  |
|                             | Size (d): 185.8 nm                                       |                                  |            |
|                             | Entrapment capability: 62 %                             |                                  |            |
| PLGA/PLA nanoparticles      | chemical: PLGA (coencapsulated QUR and tamoxifen)       | Enhance in cell cytotoxicity     | [185,186]  |
|                             | Size (d): 185.3 nm                                       |                                  |            |
|                             | Entrapment capability: 68.60 %                          |                                  |            |
| Solid lipid nanoparticles   | Chemical: Trilaurin and phospholipid                    | Improve aqueous solubility       | [187]      |
|                             | Size (d): 74.61 nm                                       |                                  |            |
|                             | Entrapment capability: 83.27 %                          |                                  |            |
| Micelles                    | Chemical: Nano micelles                                | Reduced cell viability at 72 h   | [146,188]  |
|                             | Size (d): 15.4–18.0 nm                                  |                                  |            |
|                             | Entrapment capability: ≥ 89 %                           |                                  |            |
| Liposome                    | Lecithin, Cholesterol, Polyethylene glycol (PEG 4000 and QUR) | Decreased collagen deposition and lung fibrosis areas after two weeks | [151]      |
|                             | Size (d): ≥ 90 nm                                       |                                  |            |
| Liposome                    | QUR, PEG-4000                                          | Anti-angiogenesis and anti-tumor effects | [189]      |
| Liposome                    | Cholesterol, egg sphingomyelin, QUR, PEG 2000-ceramide, and vincristine | No bodyweight loss and inhibited tumor xenograft | [190]      |
| Lipid nanocapsules          | Solunol, Lipophile WL, 1349, QUR, and Phospholipon     | Improve solubility (aqueous) by a factor of 100 | [156]      |
| Nanostructured lipid carriers | Steric acid, glyceryl monostearate, soya lecithin, media chain triglyceride, and QUR | Enhanced the QUR retention in dermis and epidermis by 3.03 and 1.52 times | [155]      |
| Solid lipid nanoparticles   | Soya lecithin, glyceryl monostearate, PEG 400, QUR, and Tween-80 | Cmax increased up to 12.22 μg/mL, AUC(0-1) increased up to 5.71-fold | [191]      |
| Complex                     | Phospholipid and QUR                                   | Improve the anti-oxidant activity, Improve water solubility by 12 folds | [157]      |

Note: PLA, poly (D, L-lactic acid); PLGA, poly(lactic-co-glycolic acid); WPI, whey protein isolate; QUR, quercetin; LRA, lotus root amylopectin.

### 4.3. QUR nanocrystals

QUR nanocrystals have exhibited novel physicochemical characteristics in diverse disciplines. Some primary properties include the escalated ability to transport easily through a cell membrane. Different applications of nanocrystals are administrated via various routes, for instance peroral [118], parenteral [119], pulmonary, ocular [120], dermal [121]. Additionally, owing to the larger surface area, the higher dissolution rate of these drug nanocrystals is also improving their application spectrum, contributing positively to bioavailability [122]. Among these techniques used for production include both the “bottom-up” and “top-down” processes classified as per the principle employed in their production [123]. Commonly used “top-down” methods include bead milling and high-pressure homogenization. Higher energy input and lower power efficiency with no harsh solvents employed are the highlights of these methods [124]. Precipitation is the foremost technique of “bottom-up”. It is also coupled up with some “top-down” methods including homogenization primarily to prevent the growth of precipitated nanocrystals to microcrystals. This technique is known as “caviprecipitation” [125].

Caviprecipitation, bead milling, and homogenization have been used to prepare the QUR nanocrystals with bead milling manifesting the smallest particle size while high-pressure homogenization produced the lowest polydispersity index [126]. The caviprecipitated product is reported to have a larger particle size along with increased saturation solubility owing to the ethanol present inside. However, the zeta potential of all the other products showed stability other than the caviprecipitated one.

Previous research compared the high homogenization press process (HPH) and evaporative precipitation into the aqueous solution (EPAS) process to analyze the feasibility of each process in the formation of chemically stable QUR nanosuspension [127]. There was no alteration observed in the crystalline state of QUR with the HPH process while a crystalline to the amorphous transition phase was seen through the EPAS process. Additionally, a higher improvement was also observed in terms of solubility and dissolution rate as compared to HPH suspension owing to the higher inner energy linked to the amorphous phase. Tremendous improvement in both the chemical and photo-stability of nanosuspension of QUR molecules was observed when compared with the solution. Further research indicated that QUR-loaded nanosuspension (QUR-NS) was produced by the HPH method and a tandem of nano-precipitation (NP) [128]. The QUR solubility in suspension form was enhanced about 70 times as compared to the crude QUR. Similarly, the dissolution of QUR from QUR-NS also escalated as compared to the primary QUR powder. In plasmas form, QUR-NS showed a significant decrease in the clearance rate (2 ± 0.2 mL/min vs. 15 ± 3 mL/min) while an increase in the area under the curve, the plasma concentration-time (AUC) (53996 ± 4125 µg/mL/min versus 3471 ± 110.2 µg/mL).
4.4. QUR loaded polymeric micelle

Researchers also focused on polymeric micelles for injecting drug delivery in the systemic circulation [129]. This method is characterized by a longer retention time, high tissue permeability and is also associated with a focus on diseased tissue to enhance passive targeting [130,131]. Owing to the solubility, biocompatibility, and stability properties, polymeric micelles are given significant importance in the oral administration of QUR.

In polymeric micelles, the inner ‘core’ and outer ‘shell’ form the amphiphilic copolymers of hydrophilic and hydrophobic chains, capable of self-assembly in water present in critical micelle concentration (CMC). This micelle encapsulates the hydrophobic drug into its core, delivering it to the targeted site with higher bioavailability than the pure drug. It also prevents the degradation and metabolism of the drug in the GI tract [132,133]. Therefore, better permeability and retention rates are expected with polymeric micelle NPs. These polymeric micelles are considered perfect candidates for anticancer drug delivery, mainly by amphiphilic micelles, with major applications for QUR formulations [134-136]. Moreover, QUR loaded into nano-sized polymeric micelles with amphiphilic polymers solusplus using a modified film dispersion model, exhibited sustained release for up to 10 days in vitro with high bioavailability [137].

Another study involved nano-polymeric microspheres formed with the spray-dried method using synthesized amphiphilic CTS were loaded with hydrophobic QUR and paclitaxel for pulmonary drug delivery. It exhibited sustained releasing effects along with higher retention of paclitaxel in vivo [138]. Furthermore, mixed micelle polymeric prepared with QUR via hydration method for breast, ovarian, and multidrug-resistant cancers, resulted in improving the drug delivery along with solubility of QUR for in vitro experiments [139]. Another study indicated better cytotoxicity of QUR-SPION loaded micelles by HepG2.2.15 cancer cells. For hepatocellular carcinoma, QUR-loaded SPION micelles exhibited better vehicle properties and cell cycle arrest at the G0/G1 phase [140].

In another study, lecithin-stabilized polymeric micelles were also designed for QUR delivery against tumor activities. The optimal combination resulted in lowering the IC50 values against MCF-7, SKBR-3, and MDA-MB-231 breast cancer cells (human). Similar results were also obtained for CT26 mouse colon cancer cells, administered intravenously for animal studies. The oral and intravenous administration of QUR showed 158 % and 360 % bioavailability as compared to the absolute bioavailability (5.13%). This study confirmed the properties of QUR loaded with stabilized lecithin nanocarrier for enhancing antitumor efficacy against chemotherapy and systemic toxicities [141]. Additionally, the QUR-chitosan conjugate was employed for the delivery of doxorubicin (anti-cancer drug) and determined that the conjugate micelles can improve the cellular uptake of the drug to 2.2 folds higher as compared to the free drug accumulation. Higher permeability co-efficient with better epithelial electrical resistance for Caco-2 cells was also observed, indicating the conjugate as a promising carrier for oral delivery of anticancer drugs [142]. Moreover, QUR-cRGDK-PM (QUR loaded in ChGDK-PM) significantly optimized the therapeutic efficiency of Chinese medicinal herbs and reduces systemic and pulmonary toxicities [143]. Other antitumor activities of QUR with polymeric micelles are also an emerging research domain to further improve the bioavailability of the targeted drug. [144-146].

4.5. Glucan-QUR conjugate

Chitin glucan conjugate (ChGC) is a non-toxic, water-insoluble, and high-water absorption capacity containing polysaccharides found in yeasts and fungal cell walls. Due to its biocompatibility, it is used for various biomedical, pharmaceutical, and engineering applications. In a study, curcumin-loaded chitin-glucan QUR conjugate was used for anticancer activity. The entrapment efficiency of the conjugate was 77.32%, measured via pelleting. Faster drug elution was estimated in an acidic environment, as the chitin-glucan polymer swelled up owing to the anime group protonation. Results also indicated a significant cytotoxic effect against the J774 cancer cell line. Nonetheless, the anticancer potential of ChGCQ and curcumin-loaded ChGC QUR conjugate needs further research in chemotherapy and pharmaceuticals [147].

Singh, Dutta, Kumar, Kureel and Rai [148] also synthesized chitin-glucan-aldehyde-QUR conjugate through the condensation reaction. This conjugate exhibited strong antioxidant properties with anticancer activities on macrophage cancer cell lines (J774). Strong biocompatibility was also ascertained in the peripheral blood mononuclear cells (PMBCs). The cytotoxicity was observed only against the J774 cell line but no activity for PMBCs was determined.

4.6. Phospholipid and liposomes formulations

Active QUR is delivered by different formulations lipid-based including liposomes, lipid nanoparticles, phospholipid complex, etc. [Fig. 3]. Liposomes are small spherical lipid bilayer vehicles enclosed in an aqueous compartment [149]. These liposomes shelter the drugs against external stimuli along with improving the water insolubility and enhancing the overall drug-delivering efficacy [150]. Anticancer drugs are also reported to have enhanced efficacy owing to the extended exposure of the drug to the tumor site during the prolonged circulation time. Additionally, enhanced permeability and retention effect also resulted in preferential accumulation of the anti-cancer drugs in the tumor. Liposomal QUR was prepared successfully against the in vivo bleomycin-induced pulmonary fibrosis [151]. This liposomal QUR decreased the increase of total cell counts along with macrophage counts in the bronchial veolar lavage fluid. The neutrophil and lymphocyte count decreased significantly on days 7 and 14 after the liposomal QUR injection (p < 0.05). This treatment also reduced the hydroxyproline content (approx. 35.8%) as compared to the bleomycininduced group (p < 0.05). Another research highlighted the QUR liposomes contribution in lessening the lung fibrosis areas and deposition of collagen along with decreasing the expression of transforming growth factor (TGF-1), as per the histopathological assessments. The therapeutic efficacy of QUR liposomes also contributes to combating the arsenic toxicity mediated oxidative damage reported in both hepatocytes and brain cells in rat models [152].

Liposomal QUR was found most potent for complete prevention of arsenite-induced reduction in antioxidant levels in the liver and brain of rats. Solid lipid nanoparticles (SLNs) are submicron’s type drug delivery system are gaining attention. Solid lipids employed are both from natural and synthetic sources with the main advantages include high biocompatibility, high bioavailability, controlled release mechanism, and using oral, intravenous, pulmonary, and transdermal routes of administration [153]. Recent studies indicate that SLNs with 13.2% QUR drug-loaded resulted in a slow release of over 48 h enhancing the oral bioavailability in the rat’s plasma. The maximum concentration (Cmax) value of QUR in SLNs (12.21 ± 2.14 μg/mL) was estimated to be higher than that obtained with QUR entrapped in sodium carboxymethyl cellulose suspension (5.91 ± 1.23 μg/mL) after a single dose of 50 mg/kg. After the oral provision of QUR-SLNs suspension for 48 h, the QUR plasma concentration was reported to be still more than 2 μg/mL, while it went unidentified at 16 h for QUR suspension. Dhawan, Kapil and Singh [154] formulated the SLNs of QUR using cornprotol as the lipid with Tween 80 being used as the surfactant. Overviewing the in vivo behavioral and biochemical analysis, better memory retention was observed in the rats treated with SLN-encapsulated QUR than pure QUR-treated rats.

Emulsion evaporation solidification was carried out at low temperatures to produce QUR-loaded nanostructured lipid carriers (QUR-NLCs)
could also escalate the permeation of QUR, increase the concentration
plex has a fluffy, porous, and rough surface in SEM with 12 times higher
functions. Skin histological studies revealed that the skin stratum cor-
neum treated with QUR-NLCs was more scattered and loose as compared
to that treated with QUR propylene glycol solution. Concluding that
QUR-NLCs could also contribute to the weakening of the barrier function
of stratum corneum along with promoting the drug permeation.

Flavonoid-loaded lipid nanocapsules (LNC) were designed and
characterized with encapsulation of QUR in LNC resulting in increasing
its apparent aqueous solubility by a factor of 100 [156]. QUR alignment
at this LNC interface between oil and hydrophilic polyethylene glycol
moieties of the surfactant with high stability of 10 weeks was reported as
per the recent studies without any oxidation. Furthermore, to enhance
the absorption of quercetin through the gastrointestinal tract a quercetin
complex was prepared with phospholipid (QUR-PC) [157]. This com-
plex has a fluffy, porous, and rough surface in SEM with 12 times higher
water solubility reported in the complex from 3.43 μg/mL to 36.80 μg/
ML. Analysis of in vitro antioxidation activity of crude quercetin and
quercetin complex indicated that no statistical differences were
observed highlighting the lack of the complexation process’s impact on
the bioactive ingredient’s bioactivity.

4.7. QUR loaded mucoadhesive nanoeumulsions

So far, limited research has been reported with QUR-loaded
mucoadhesive nanoeumulsions (QMNE). QMNE is considered a novel,
effective, non-invasive, and safe delivery system for brain targeting for
cerebral ischemia treatment [158]. In a study, intranasal delivery of
QMNE was researched with a mean globule size of 91.63 ± 4.36 nm, the
zeta potential of −17.26 mV, drug content 99.84, and viscosity of 121
cp. Enhanced bioavailability of QUR was found along with better neu-
robehavioral activity in terms of locomotion and grip strength, histo-
pathology, and reduced infarction volume effects in middle cerebral
artery occlusion (MCAO)-induced ischemic rat models. The research
concluded high brain targeting potential, better formulation efficiency,
effective targeting capability of QMNE [158]. However, further
clinical and pre-clinical trials are needed to prepare the formulations
that can further strengthen the low risk and higher benefit ratio for the
patients in different diseases

5. Conclusion and future prospect

QUR is a phytochemical with beneficial health benefits against
different diseases. However, some studies proved its poor absorption in
the human body. Recently innovative strategies have been proposed
which enhanced QUR bioactivity in humans, lower costs, and are better
described during clinical examinations. Researchers also designed novel
extraction methods that provide a better extraction yield of QUR.
Moreover, future work can be focused on minimizing the limitations of
the aforementioned methods, and integration of one or more extraction
methods is also an option to improve the results. In recent years, some
non-invasive methods were also established for the evaluation of QUR
from agricultural products. These methods are fast, non-destructive,
environmentally friendly, and online detection is possible. However,
improvement in the weaknesses of these techniques can expand their
applications in more research domains. For example, strategies to deal
with auto fluorescence issues in fluorescence spectroscopy, methods to
resolve scattering phenomenon in terahertz spectroscopy, designing of
new chemometric models, and improvement in near-infrared spectro-
copy ability to detect volatile compounds in food can extend its appli-
cations. Also, algorithms for rapid processing of raw data and techniques
to deal with data mining can make hyperspectral imaging a more effi-
cient tool, while stable, reproducible, while sensitive nanoparticles can
make surface-enhanced Raman spectroscopy a more sensitive and reli-
able sensing platform. Besides, integration of these non-interruptive
methods can also make a more accurate, sensitive, and fast analytical
tool for the detection of phytochemicals from different fruits and
vegetables.

CRediT authorship contribution statement

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original draft. Rabia Siddique: Data curation, Writing – original draft.
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Xu: Supervision, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial
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