Advances in Colloid and Interface Science 318 (2023) 102938

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Historical Perspective

Biofunctionalization of natural extracts, trends in biological activity and kinetic release

Abraham Osiris Martínez-Olivo [a], Víctor Manuel Zamora-Gasga [a], Luis Medina-Torres [b], Alejandro Pérez-Larios [c], Sonia Guadalupe Sáyago-Ayerdi [a], Jorge Alberto Sánchez-Burgos [a,*]

[a] Tecnológico Nacional de México/Instituto Tecnológico de Tepic, Av. Tecnológico 2595, C.P. 63175 Tepic, Nayarit, Mexico
[b] Facultad de Química, Universidad Nacional Autónoma de México, C.P. 04510 Ciudad de México, Mexico
[c] Universidad de Guadalajara, Centro Universitario de los Altos, División de Ciencias Agropecuarias e Ingenierías, Laboratorio de Materiales, Agua y Energía, Av. Rafael Casillas Aceves 1200, C.P. 47600, Tepatitlán de Morelos, Mexico

ARTICLE INFO

Keywords:
Extract
Biological activity
Functionalization
Toxicity
Pharmacokinetics

ABSTRACT

The health benefits provided by plant matrices is due to the presence of certain compounds that, in studies carried out in vitro and in vivo, have shown to have biological activity in certain conditions, not only as a natural treatment against various conditions, but also for the quality of preventing chronic diseases, these compounds, already identified and studied, they can increase their biological function by undergoing structural chemical modifications or by being incorporated into polymer matrices that allow, in the first instance, to protect said compound and increase its bioaccessibility, as well as to preserve or increase the biological effects. Although the stabilization of compounds is an important aspect, it is also the study of the kinetic parameters of the system that contains them, since, due to these studies, the potential application to these systems can be designated. In this review we will address some of the work focused on obtaining compounds with biological activity from plant sources, the functionalization of extracts through double emulsions and nanoemulsions, as well as their toxicity and finally the pharmacokinetic aspects of entrapment systems.

1. Introduction

Chronic diseases such as cancer, diabetes, hypertension, cardiovascular problems, Alzheimer's, among others, are a problem of constant exploration in the field of science and research, they are currently the largest cause of deaths worldwide [6]. Although there are treatments for these conditions, the results are not always favorable, due to the aggressive and invasive procedures used, as well as the use of drugs with prominent side effects [62]. There is evidence of the possible prevention of such illnesses by eating a healthy diet, exercise and under stress [19], however, it is not always possible to meet these requirements, either due to the busy pace of life, little accessibility to natural and healthy foods or simple misinformation in the consumption of the diet. As it does not have at its disposal foods that comply not only with nutrition, but can also provide a benefit to the consumer thanks to the presence of compounds with biological potential (antioxidant, anti-inflammatory, hypoglycemic, anticancer, etc.), the consumption of extracts of natural origin from medicinal plants or by-products of fruits and vegetables has been chosen as an alternative, this is of wide importance since beyond the search for a therapeutic treatment, the consumption of bioactives from natural sources can promote the prevention of the development of these conditions [68]. Abundant natural sources of bioactive compounds have been identified; plants and fruits of which there is a record in the use of treatments of various ailments, this because these plant matrices have compounds with some beneficial biological activity [59], however, these compounds, when extracted from the plant matrix, can be susceptible to external conditions (pH, presence of light, humidity in case of dehydrated extracts, among others) [10], so it is easy to request their functional properties, at this point the biofunctionalization of natural extracts enters, through structural modifications and entrapments of compounds in biodegradable polymers [11,13], facilitates the handling and stability of the extracted compounds, minimizes unwanted reactions avoiding the loss of activity and being one of the most important aspects, allows a controlled release of bioactive compounds. The controlled release of encapsulated compounds is the cornerstone of research in the development of entrapment systems, from drugs and drugs to nutraceuticals, the study of the kinetic parameters of release allows to establish the efficiency of the system, by allowing not only the release at

* Corresponding author.
E-mail address: jsanchezb@tepic.tecnm.edu.mx (J.A. Sánchez-Burgos).

https://doi.org/10.1016/j.cis.2023.102938
Received in revised form 23 May 2023;
Available online 8 June 2023

a certain time, but also to establish the dosage and concentration in which this compound can act at the time of being bioavailable in the organism [12], aspects such as release speed, latency time, release constant, minimum effective concentration and maximum safe concentration, provides valuable information when designating an application to an encapsulated compound. In this review we will review some of the works focused on obtaining natural extracts of plants or by-products, the biofunctionalization of extracts by obtaining double emulsions, Nanoemulsions and Nanocomposes, the controlled release of encapsulated compounds, as well as the study of their kinetic parameters and the biological activity of compounds obtained from natural extracts; as well as some complementary analyses in silico.

2. Natural plant extracts and their biological activity

The extraction of compounds from plant matrices is an art that has been developed since the origins of civilization, with maceration, leaching and infusion being the oldest conventional methods on record [71], however, at present various extraction methods have been developed with deep eutectic solvents (DEP) and through emerging technologies that favor a greater yield in obtaining extracts with functional properties. In this sense, ultrasound (UAE), high hydrostatic pressures (APH) and supercritical fluids (FSC) have marked a pinnacle as environmentally friendly technologies, since polluting solvents are not used, the production of wastewater is minimized and clear allowing efficient extraction without structurally affecting the chemical and functional properties of the compounds [73]. Emphasizing this last point, the extraction of compounds with functional biological potential is the order of the day in terms of the search for alternatives for the treatment or prevention of chronic diseases (cancer, diabetes, hypertension, Alzheimer's, among others) [63], compounds obtained from natural sources have shown an important beneficial effect on health, not only for the antioxidant capacity of these same, but also for the effect on the prevention of some chronic conditions [69]. Although by itself, the frequent consumption of fruits and vegetables can guarantee good health [5], in recent decades a potential has been found in obtaining extracts with functional properties from agro-industrial by-products, an example of this is the obtaining of an extract of polyphenols (PP) from orange peel, using a DEP from choline chloride and ethylene glycol, an extract was obtained in which compounds were identified by high-performance liquid chromatography (HPLC) ferulic acid as the predominant compound; as well as ρ-coumaric acid and gallic acid [48]. On the other hand, flavonoids such as catechin and epicatechin have been identified in sorghum millet, being the most abundant, and to a lesser extent p-coumaric, ferulic, caffeic and protocateonic acid [75]. Although agro-industrial by-products have been classified as one of the best sources in obtaining bioactive compounds, it has also been possible to extract bioactive compounds from woody plant material, since it has been proven that compounds with antioxidant, antibacterial, anti-inflammatory, antitumor, etc. activity are found in the bark of trees [67]. Table 1 shows some of the reports on the extraction of bioactive compounds from plant sources; as well as the extraction method used in obtaining them and the potential biological activity of the aforementioned ones.

Now, the biological activity of the compounds extracted from plant matrices is of the most interesting for human health, it is also important to take into account the bioaccessibility of the same, since once removed from the matrix that contains them, they can be exposed to gastric conditions and lose their biological function, so it is necessary to incorporate the compounds in polymer matrices, in order to maintain or in greater preference, increase this activity, this process is known as biofunctionalization.

Table 1
Compounds extracted from plant matrices, extraction method and biological activity.

Compound	Plant matrix	Extraction method	Biological activity	Reference
Quercetin-3-O-β-D-gluco-pyranoside (isoquercitrin) as a compound of greater abundance	Petals of *Rosa x damascena* Mill.	Maceration and ethanolic extraction	Antioxidant capacity by DPPH methods 94.11 ± 0.01%, CUPRAC 555.316 ± 0.06 μmol ETrolox/mL, FRAP (354.43 ± 0.03 μmol ETrolox/mL and ABTS 76.351 ± 0.02 μmol Trolox/mL	[23]
1-methyl-1H-pyrrole as the most abundant compound	Leaves of *Pistacia vera* L.	Ultrasonic bath	Antioxidant capacity of male leaves by the method of DPPH 644.36 ± 31.20 mg ETrolox/g of dry extract, ABTS 1394.95 ± 5.49 mg ETrolox/g of dry extract and FRAP 808.24 ± 18.13 ETrolox/g of dry extract. Antioxidant capacity in female leaves by the method of DPPH 704.53 ± 14.16 ETrolox/g of dry extract, ABTS 1334.35 ± 14.16 ETrolox/g of dry extract and FRAP 521.52 ± 4.11 ETrolox/g of dry extract.	[21]
Quercetin	Leaves of *Cnidoscolus aconitifolius* Mill	Extraction by Soxhlet using ethyl acetate	Inhibition of inflammation in mouse ear of 23.52% for a dose of 25 mg/kg and 49.41% for a dose of 50 mg/kg	[49]
Quercetin-O-glucuronide as the most abundant compound	Healthy green leaves from a clone of *Vitis vinifera*	Orbital agitation extraction using a solvent of 75% (v/v) methanol / 0.05% (v/v) trifluoroacetic Acid	Complete inhibition in HSV-1 replication in pre-treatment trial of the virus with concentration of 10 μg/mL and 80% inhibition in SARS-CoV-2 at a concentration of 10 μg/mL	[80]
Unidentified phenolic compounds	Seaweed *Sargassum vachellianum*	Ethanol extraction	42.21 ± 0.32% inhibition of hydroxyl radical (-OH) and 40.88 ± 0.15% inhibition of hydrogen peroxide radical, both at a concentration of 1000 μg/mL	[28]
Squalene as a compound of greater abundance	Leaves of *Hemigraphis colorata*	Soxhlet extraction using hexane as a solvent	Inhibition halo of 22 mm against *E. coli*, 24 mm of inhibition against *Salmonella typhi*, 15 mm of inhibition for *Klebsiella* sp., 10 mm of inhibition in *S. aureus* and 20 mm against. *Pseudomonas*. Antioxidant capacity by METHOD of DPPH 26.66 ± 0.57%; 39.00 ± 1.0% and 70.06 ± 0.57% at concentrations of 1, 5 and 7.5 mg/mL respectively.	[58]
Volatile organic compounds such as benzyl cyanide, benzyl thiocyanate, benzyl isothiocyanate and benzaldehyde	Sedes of *Lepidium sativum* L.	Supercritical fluid extraction	Antioxidant capacity by DPPH IC50 925 ± 7 μg/mL. 16 mm of inhibition halo in *S. epidermidis*	[55]
Gallic acid as a compound of greater abundance	Fruits of *Physalis peruviana* L.	Ethanol extraction	Antioxidant capacity by the DPPH method 72.82% inhibition at a concentration of 150 μg/mL. Antimicrobial activity against *Bacillus cereus* (ATCC 33018) with 17.15 ± 0.16 mm of inhibition halo.	[20]

3. Biofunctionalization of natural extracts

As mentioned above, compounds extracted from plant sources have interesting biological activity of interest in human health, coupled with this, the physical and chemical characteristics that these possess, allow interaction with various molecules, due to their versatility [77], can be used in the synthesis of nanocomposites, biofilms, capsules, or in the formation of colloids such as single or double emulsions, Hydrogels and a wide variety of materials, all these structural chemical modifications to biological compounds are called biofunctionalization. Thanks to these modifications, the biological activity of the compounds can be maintained or increased, improve bioaccessibility and controlled release, as well as avoid unwanted interactions that may intervene with their biological effect. Of the most remarkable biofunctionalization methods are double emulsions, nanoemulsions and nanocomposites, below, we will review some of the works focused on the formulation and synthesis of the aforementioned ones.

3.1. Double emulsions

An emulsion is the dispersion of an aqueous or oily phase in a continuous phase of opposite polarity, existing water-oil (W/O) and oil-water (O/W) emulsions, while a double emulsion consists of the generation of a primary emulsion either W/O or O/W dispersed in a second continuous phase, to obtain a double emulsion of water-oil-water (W_1/O/W_2) or oil-water-oil (O_1/W/O_2) [30,38], the latter allow improved protection and controlled release unlike simple emulsions, thanks to the multiple compartmental design that characterizes them. For this type of system, the selection of the oil phase plays an essential role when designing the double emulsion, since, in most cases, it is chosen to use essential oils as a nuclear or interfacial oil phase, while, in other cases, the selected oil serves as a transport vehicle when it is desired to functionalize a lipophilic compound such as carotenoids or fatty acids [56], as well as some vitamins (vitamin A and vitamin E) [32]. Another aspect of great nature, is the surfactant, this allows the generation of the emulsion by preventing the phenomenon of coalescence from occurring, allows the electrostatic stability of the phases and decreases the surface tension. Surfactants are classified into anionic (sodium dodecylsulfate) [36], cationic (Hexadecyltrimethylammonium bromide) [29], amphoteric (lecithin) [70] and non-ionic (polysorbate 20 and 80) [26], in many reports proteins are used as surfactants either soy protein [76], milk protein [64] or some proteins obtained from forest by-products such as olive leaf [57]. Double emulsions allow the functionalization of more than one compound or extract, since in each of the multiple phases they can be incorporated without problems, thus achieving a controlled release of bioactives in the different stages of release for which it was designed. This encapsulation method also allows the manipulation and application of compounds such as anthocyanins; in an emulsion designed from elderberry extract (anthocyanin extract) using palm oil as an interfacial oily phase (W/O/W) with potential application in food to prolong color life in food matrices [14]. Although double emulsions are thermodynamically unstable systems, strategies have been found to maintain the stability of the system, reinforce the interfaces of the W/O and O/W emulsion, using whey protein combined with some type of rubber [53], Polyvinyl alcohol as a stabilizer [51] or polylactide-colicolida as a coating material [79]. Strategic substitutions in the composition of the oil phase can serve not only as a stabilizer of the system, but also as carriers of antioxidant compounds, olive, flaxseed and fish oils are not only very frequently used in the design of double emulsions, but also provide polyunsaturated fatty acids [57] giving functionality to the double emulsion. Even the proper formulation of a double emulsion has the particularity of being incorporated into complex food matrices, increasing the presence of polyphenols and therefore conferring a greater antioxidant capacity [17], so they could be considered as functional ingredients.

3.2. Nanoemulsions

The particle or droplet size is what defines this type of entrapment systems, although the classification may vary between literatures, based on the magnitude of one nanometer, it can be considered nano to all that emulsion that presents a droplet size <1000 nm [54]. This size plays an important role when designing an emulsion system, because it can result in greater bioactivity or greater toxicity [40] Table 2 presents some of the toxicological studies aimed at nanoemulsion systems. Entering into this last point, there has been some controversy regarding the toxicity of nano-sized encapsulating systems; however, nanoemulsions, whether double or single, have shown greater bioactivity at the cellular level [72], and may have applications in the field of medicine or in the treatment of patients, even as protective agents in chemotherapies, the following table shows some cell studies of nanoemulsions. To obtain nanometric emulsions, ultrasound and microfluidization equipment have been used; the first, thanks to the phenomenon of cavitation caused by ultrasound waves, allows the obtaining of nanometric droplet sizes at the time of generating the implosion of larger droplets, in addition to a more uniform homogenization at the time of applying said treatment [3]. However, the application of prolonged ultrasound times to the system generates heat, due to the release of energy that occurs at the time of cavitation, causing in the first instance, the coalescence of the emulsion and in the second term the partial or total degradation of the components of the system [7,15,78]; loss of activity of the bioactive compound due to structural chemical modifications [81], denaturation of proteins [34] in case of containing it in some part of the system and the oxidation of fatty acids of the oily phase [11,13]. Despite these implications to take into account when generating ultrasonic nanoemulsions, it remains one of the widely used methods for obtaining nanoemulsions. The second method, microfluidization, favors the obtaining of more homogeneous particle sizes [50], through the coalition of the phases to flow changes in the flow the formation of the emulsion is achieved, by not using extreme conditions in the equipment, there is no loss of compounds, however, one of the greatest implications in this method, they are not technical issues, but the high cost of the equipment. Something that characterizes nanoemulsions is that they possess the quality of expansion in various areas, either from the addition in the formulation of films for fruits and vegetables [61], as carriers of compounds with therapeutic potential [33] and cosmetics [22,25].

3.3. Nanocomposites

The composite materials consist of two components, matrix and reinforcement, added a third called interface, which is formed from the interaction of the first mentioned. The matrix is the continuous phase, where the reinforcement is dispersed, in which the physical, chemical and functional properties of the composite fall. This matrix can be metallic, polymeric or ceramic, which classifies the composite depending on the matrix. The reinforcement is the dispersed part of the composite, where the mechanical load falls or modifies some property to improve the functionality of the material. This can be organic or inorganic of natural or synthetic origin. While the interface originates from the interaction that exists between the matrix and the reinforcement, this interface is responsible for the transfer of load from the reinforcement to the matrix. This is the compatibility and synergy, establishing the electrical and thermal continuity between both phases. For a material to be considered nanocomposite, it must have at least one of its three dimensions a scale of 1–100 nm, whether nanoparticles (3 nanometric dimensions), nanotubes (2 dimensions) or nanosheets (1 or 2 dimensions) [47]. Nanoparticles are synthesized from metals or metal oxides, and can be categorized into nanocrystals, nanogranules, or isodimensional nanoparticles. Nanoparticles of metals such as copper [45], metal oxides such as ferrous oxide and silver [1], ferric oxide and zinc [39], zinc and copper oxide [43] have been synthesized. On the other hand, carbon nanotubes have been a promising nanomaterial in various

Table 2
Toxicological studies in nanoemulsion systems.

Type of emulsion	Encapsulated compound	Cell line	Contribution	Reference
Oil in water (O/W)	Eugenol	HIEC-6 (Human Intestinal Epithelial Cell Line) of ATCC	28–47% toxicity.	[44]
Water in oil (W/O)	Tincture of *Nigella Sativa* L.	Ovarian Cancer and Umbilical Vein Endothelial Cell Line A2780 (HUVEC)	Cancer cells A2780 IC_{50} 0.72 μg/mL HUVEC IC_{50} cells >25 μg/mL	[9]
Oil in water (O/W)	Vitamin D	Caco-2 human colorectal adenocarcinoma cell line	Cell viability >80%	[72]
Water in oil (W/O)	β-caroten	Monolayer model of Caco-2 cells of human colorectal adenocarcinoma	100% integrity of cells exposed to nanoemulsions	[74]
Oil in water (O/W) incorporated in chitosan hydrogels and xanthan gum	Vitamin D_3 and curcumin	Human nasal cell line RPMI 2650 (CCL-30)	80% cell viability at concentrations <1 mg/mL	[18]
Oil in water (O/W)	Soy lecithin	Skin of healthy anonymous female and male donors (middle-aged between 20 and 65 years) obtained from talk surgeries (abdomen, back, breast)	Viability >60% of keratinocytes	[70]
Oil in water (O/W)	Brinzolamide	Adult human retinal pigment epithelial cells (ARPE-19, ATCC, USA)	Inhibition of 50% of ARPE-19 cells in incubation from 1 to 24 h.	[37]

application areas, due to their strength 10 to 100 times higher than steel and an amazing thermal resistance of up to 2800°C in vacuum [4], although this depends on their chemical composition [66], however, due to its low solution in aqueous and organic solvents, its use has been limited [46]. Finally, nanofilms have great versatility in various areas, from intelligent coatings with chitosan [31], to applications in the field of electrocatalysis [82], in addition to possessing antibacterial biological properties [8].

Although it is important to entrap and stabilize compounds obtained from plant sources to preserve or increase their biological activity, it is also important to study the kinetic parameters of encapsulation systems, since, from this study, the type of application intended for the system can be defined.

4. Release of encapsulation systems

The study of kinetic parameters understood as release speed, release time, latency time, release constant, allows to define the release behavior, whether Fickian or non-Fickian, or the type of release kinetics, this allows to deepen the release behavior of encapsulation systems [42], this is of imperative relevance, because although various investigations have been carried out focused on the encapsulation of compounds and their characterization, the release of said compound is usually left aside, which in greater instances, is the purpose when designing an entrapment system, in short, the system allows to stabilize the compound and this is released at the time it is required. To understand the vast panorama provided by the pharmacokinetic study of compounds, the main basis by which this phenomenon is governed must be understood. Fick's law says that "the particles in greater concentration in a phase, tend to migrate to the phase of lower concentration until reaching a balance in the concentration of these" [16], the release systems that are governed by this law, are in systems of Fickian behavior, that is, the release is governed by diffusion; being a constant release and velocity referring to kinetic time; while those systems where in the first instance there is an erosion of the outermost layer of the system and subsequent a diffusion of the particles, are classified as non-Fickian behavior, this type of behavior is characteristic of hydrogels [60].

To calculate the rate of release, a sum of the quotient is made the concentration gradient of the drug or compound and the gradient of release time; as expressed in the following equation:

$$k = \Sigma\left(\frac{\Delta C}{\Delta t}\right) \tag{1}$$

Where: ΔC is the increase in the concentration of the drug or compound and Δt is the release time.

Once the rate of release is calculated, the Korsmeyer-Peppas equation is applied [24], which describes the law of power, this is a semi-empirical equation:

$$f_1 = \frac{M_i}{M_\infty} = Kt^n \tag{2}$$

where f_1 is the amount of drug released, M_∞ is the amount of drug in the steady state (value close to the amount of drug contained at the beginning of the release process), M_i is the amount of drug released over time t, K is the constant of release rate, and n is the exponent of release (related to the mechanism of drug release) as a function of time t. This model was developed specifically for the release of a drug molecule from a polymer matrix, such as a hydrogel. In recent years, a modified form of this equation has been employed that considers latency time (l), which marks the beginning of drug release from the system [52].:

$$\frac{M_{(i-l)}}{M_\infty} = K(t-l)^n \tag{3}$$

Or in its logarithmic form:

$$log\left(\frac{M_{(i-l)}}{M_\infty}\right) = logK + nlog(t-l) \tag{4}$$

Where M_∞ is the amount of drug in the steady state, M_i is the amount of drug released over time t, K is the release rate constant, n is the release exponent (related to the drug release mechanism) as a function of time t and l is the latency time.

This model is useful for the study of the release of compounds of polymeric systems when the mechanism of release is unknown or when more than one type of release phenomenon occurs, depending on the value of n that has a better fit in the model two cases can be presented: Fickian model (case I) and non-Fickian model [41,83]. In a Fickian model the value of $n = 0.5$, the release is governed by diffusion, according to Fick's law, the rate of release is considered constant according to the kinetic time [2]. When $n = 1$, the model is non-Fickian [35], then the kinetics belong to order zero, being driven the mechanism of release by swelling or relaxation of the polymer chains. When the phenomenon of glass transition intervenes in the process of release of the compound and there is an increase in the rate of absorption of the solvent in which the system is at the time of release, the mechanism evolves to Super Case II, where an expansion of the forces exerted by the swelling of the gel is manifested, then the value of $n > 1$, in this case, presents an extreme transport of the compound caused by the rupture of the polymeric wall of the system [27,60]. To determine the value of n, the portion of the release curve is taken into account, where $\frac{Mi}{M\infty} < 0.60$, in most cases it is considered that the release occurs in only one direction and that the glass transition temperature of the polymer does not intervene in the release process as long as it is lower than the ambient temperature. It

may be the case of a mechanism of the Fickian type in systems where the glass transition temperature is higher than the ambient temperature when a plasticization is generated in the polymer, however, these are special cases [65].

5. Perspective

The trends in relation to the biofunctionalization of natural extracts with potential biological effect are evident (Fig. 1), since the search yields works aimed at biofunctionalizing natural extracts (rosemary, cinnamon, wheatgrass, *Panax ginseng*) mainly in biopolymers such as chitosan and to a lesser extent by green chemical synthesis of metallic nanoparticles (Ag especially). For both cases, not only the toxicological attributes (safe use and biocompatibility) but also the numerous biological activities they externalize (antimicrobial, antioxidant, cytotoxicity) stand out. However, based on the search, the antimicrobial effect is emphasized, since the authors comment that it is imperative to discover new alternatives to dispense with the use of antibiotics, since bacterial resistance to these chemical substances is a phenomenon that symbolizes a crucial fact for human health. However, it is surprising the situation that today there are no reports of a biofunctionalized food matrix with natural extract (double nanoemulsion, nanocomposites) and study of its pharmacokinetic parameters that promotes, after gastrointestinal digestion, one or more beneficial effects towards health taking into account its previous characterization as a profile of bioactive compounds, bioaccessibility, fermentative capacity via colonic fermentation, because as far as we know, these points contribute substantially to the health of the host either by prophylactic or palliative effect.

Fig. 1. perspective on the functionalization of compounds from 2018 to 2022.

Therefore, it is undeniable that venturing into the generation of bio-functionalized food matrices with natural extracts is viable and attractive, not to mention that the proposals will be innovative and will open the door to future research in this interesting field.

6. Tendency

Fig. 2 shows the trends in the research used the keywords "NATURAL EXTRACT, FUNCTIONALIZATION, KINETICS OF RELEASE AND BIOLOGICAL ACTIVITY" as a search, yielding the following results, as a nuclear word in all the results of >14 thousand articles that included these keywords, it is monstro that the antioxidant activity is from which all the investigations start (red color), of which the words "hydrogel, collagen, gelatin, polysaccharide, polyphenol, wound healing" are linked. Suggesting that the trend is inclined towards the encapsulation of compounds that possess such antioxidant activity and this in turn is focused on the medical part in wound healing. In the blue cluster (lower right) it is shown that the keyword from which the rest is derived is "nanoparticles", from which the words "stability, pectins, oxidative stress, ultrasound, apoptosis, breast cancer, cancer, oral bioavailability" are linked, which shows that research is directed towards the stability and availability of this antioxidant activity focused on fighting cancer, This relates to the lower right central cluster (pink), where the words "drug delivery, pharmacokinetics, lung cancer, nanomedicine" are thrown. From the main cluster of "antioxidant activity" is derived the purple cluster (lower left) where the research focused on that keyword is shown; "antioxidant, adsorption, antimicrobial, anticancer, gold nanoparticles, nanocomposites, mechanism", indicating a trend towards the synthesis of nanomaterials with biological activity. In the upper right (green color) the last cluster of greater trend is shown, where the words "molecular coupling, phenolic compound, spectroscopy, diabetes" are observed, which suggests that much of the research focuses on the characterization and molecular coupling of polyphenols related to antioxidant activity, and a part of these, focuses on diabetes, Some isolated clusters and far from the nuclear keyword, throw interesting information on the guideline of research related to the extraction,

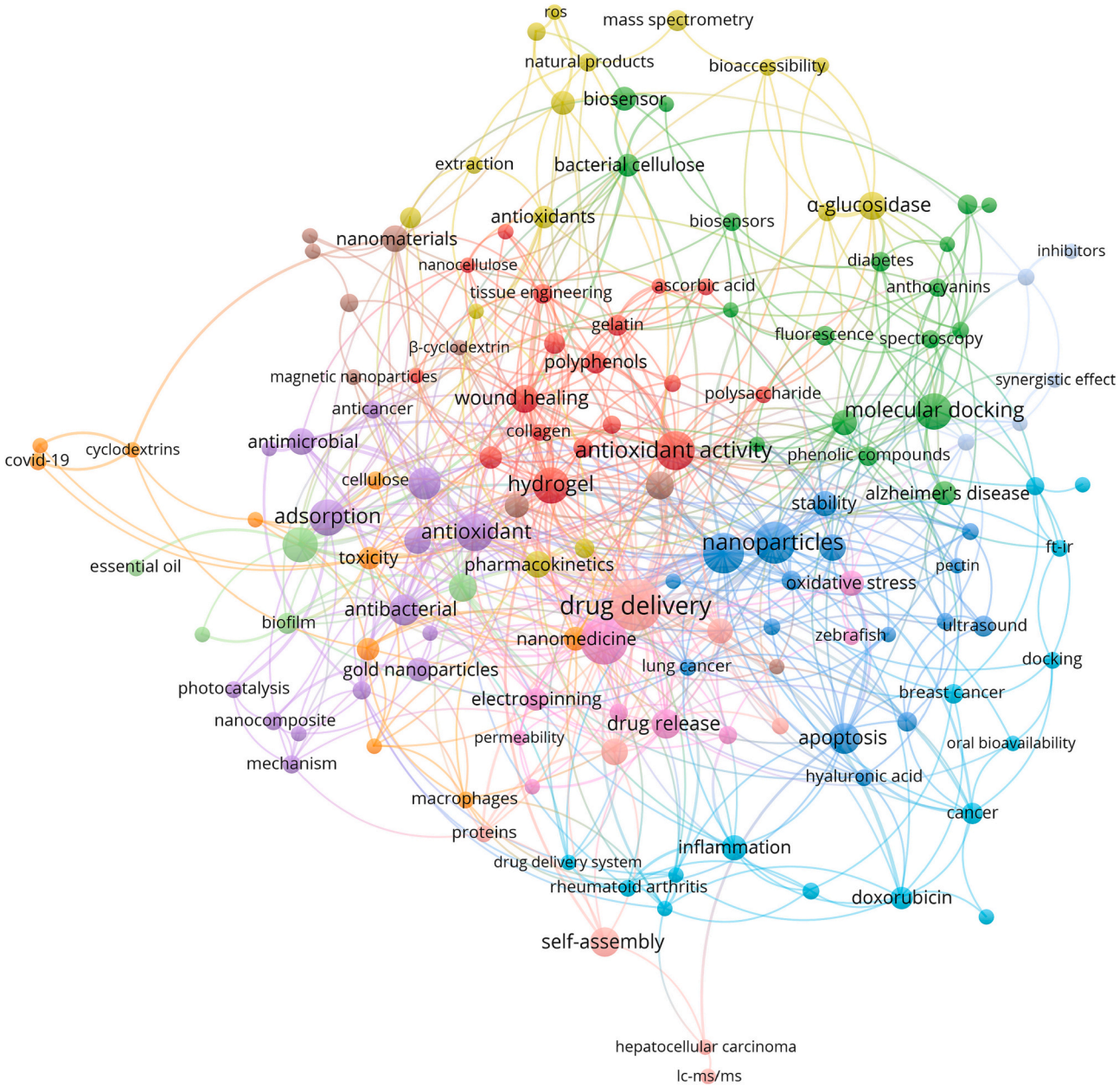

Fig. 2. Trends in the investigation of natural extracts, functionalization, kinetics of release and biological activity.

functionalization and kinetics of release of compounds of natural extracts (olive color) and some other research aimed at toxicity, cyclodextrins and covid-19 (orange color). It is clear that, in recent years, the trend towards the investigation of compounds obtained from natural matrices, focuses mainly on the antioxidant activity of these, resulting in their functionalization, seeking the stability and release of compounds with biological activity, through the synthesis of nanoparticles and nanomaterials, as well as their characterization and main anticancer application, and a part of these towards diabetes and covid-19. It should be noted that although there are many works found regarding these keywords, there are few studies that are related contemplating the extraction, synthesis, characterization and pharmacokinetics of potentially active compounds, it is expected that with this review work, there will be an overview of the current trend in the investigation of compounds obtained from natural matrices and the direction in possible future research regarding the topics reviewed.

7. Conclusion

Although there are many studies aimed at the study of the biological properties of compounds extracted from plant matrices, the functionalization of these and their morphological characterization, pharmacokinetic parameters are usually left aside, being concepts so closely related should be a fundamental part of research, this opens an opportunity in future studies for the conjugation of the three aspects reviewed in this review: extraction, functionalization and pharmacokinetics, these three aspects make up a single item in the research of natural alternative sources for the treatment and prevention of chronic diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This work was funded by the Tecnológico Nacional de México through project number 7005.19-P. Abraham Osiris Martínez-Olivo thanks the National Council of Science and Technology of Mexico for the 731287 scholarship awarded for his doctoral studies.

References

[1] Adyani SH, Soleimani E. Green synthesis of Ag/Fe3O4/RGO nanocomposites by Punica Granatum peel extract: Catalytic activity for reduction of organic pollutants. Int J Hydrogen Energy 2019;44(5):2711–30. https://doi.org/10.1016/j.ijhydene.2018.12.012.

[2] Aghili J, de Dreuzy JR, Masson R, Trenty L. A hybrid-dimensional compositional two-phase flow model in fractured porous media with phase transitions and Fickian diffusion. J Comput Phys 2021;441:110452. https://doi.org/10.1016/j.jcp.2021.110452.

[3] Ahari H, Nasiri M. Ultrasonic technique for production of nanoemulsions for food packaging purposes: A review study. Coatings 2021;11(7). https://doi.org/10.3390/coatings11070847.

[4] Ahmadi M, Zabihi O, Masoomi M, Naebe M. Synergistic effect of MWCNTs functionalization on interfacial and mechanical properties of multi-scale UHMWPE fibre reinforced epoxy composites. Compos. Sci. Technol. 2016;134:1–11. https://doi.org/10.1016/j.compscitech.2016.07.026.

[5] Altemimi A, Lakhssassi N, Baharlouei A, Watson DG, Lightfoot DA. Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. Plants 2017;6(42). https://doi.org/10.3390/plants6040042.

[6] Anderson E, Durstine JL. Physical activity, exercise, and chronic diseases: a brief review. Sports Med. Health Sci. 2019;1(1):3–10. https://doi.org/10.1016/j.smhs.2019.08.006.

[7] Anticona M, Blesa J, Lopez-Malo D, Frigola A, Esteve MJ. Effects of ultrasound-assisted extraction on physicochemical properties, bioactive compounds, and antioxidant capacity for the valorization of hybrid Mandarin peels. Food Biosci 2021;42:101185. https://doi.org/10.1016/j.fbio.2021.101185.

[8] Arabi Shamsabadi A, Sharifian M, Anasori B, Soroush M. Antimicrobial mode-of-action of colloidal Ti3C2Tx MXene nanosheets. ACS Sustain. Chem. Eng. 2018;6(12):16586–96. https://doi.org/10.1021/acssuschemeng.8b03823.

[9] Arazmjoo S, Es-Haghi A, Mahmoodzadeh H. Evaluation of anti-cancer and antioxidant properties of nanoemulsions synthesized by Nigella Sativa L. tincture. Nanomed J 2021;8(1):57–64. https://doi.org/10.22038/nmj.2021.08.06.

[10] Bazana MT, Codevilla CF, de Menezes CR. Nanoencapsulation of bioactive compounds: challenges and perspectives. Curr Opin Food Sci 2019;26:47–56. https://doi.org/10.1016/j.cofs.2019.03.005.

[11] Chen F, Zhang M, Yang C, hui.. Application of ultrasound technology in processing of ready-to-eat fresh food: A review. Ultrason Sonochem 2020;63(December 2019):104953. https://doi.org/10.1016/j.ultsonch.2019.104953.

[12] Chen P, Reed G, Jiang J, Wang Y, Sunega J, Dong R, et al. Pharmacokinetic evaluation of intravenous vitamin C: A classic pharmacokinetic study. Clin Pharmacokinet 2022;61(9):1237–49. https://doi.org/10.1007/s40262-022-01142-1.

[13] Chen WY, Lai SN, Yen CC, Jiang X, Peroulis D, Stanciu LA. Surface functionalization of Ti3C2TxMXene with highly reliable superhydrophobic protection for volatile organic compounds sensing. ACS Nano 2020;14(9):11490–501. https://doi.org/10.1021/acsnano.0c03896.

[14] Comunian TA, Ravanfar R, Alcaine SD, Abbaspourrad A. Water-in-oil-in-water emulsion obtained by glass microfluidic device for protection and heat-triggered release of natural pigments. Food Res Int 2018;106(February):945–51. https://doi.org/10.1016/j.foodres.2018.02.008.

[15] Dadi DW, Emire SA, Hagos AD, Eun JB. Effect of ultrasound-assisted extraction of Moringa stenopetala leaves on bioactive compounds and their antioxidant activity. Food Technol Biotechnol 2019;57(1):77–86. https://doi.org/10.17113/ftb.57.01.19.5877.

[16] Dayanda MA. A direct derivation of Fick's law from continuity equation for Interdiffusion in multicomponent systems. Scr Mater 2022;210. https://doi.org/10.1016/j.scriptamat.2021.114430.

[17] de Moura SCSR, Schettini GN, Garcia AO, Gallina DA, Alvim ID, Hubinger MD. Stability of Hibiscus extract encapsulated by ionic gelation incorporated in yogurt. Food Bioprocess Technol 2019;12(9):1500–15. https://doi.org/10.1007/s11947-019-02308-9.

[18] Demisli S, Mitsou E, Pletsa V, Xenakis A, Papadimitriou V. Development and study of nanoemulsions and nanoemulsion-based hydrogels for the encapsulation of lipophilic compounds. Nanomaterials 2020;10(12):1–19. https://doi.org/10.3390/nano10122464.

[19] Díez J, Bilal U, Franco M. Unique features of the Mediterranean food environment: Implications for the prevention of chronic diseases Rh: Mediterranean food environments. Eur J Clin Nutr 2019;72:71–5. https://doi.org/10.1038/s41430-018-0311-y.

[20] El-Beltagi HS, Mohamed HI, Safwat G, Gamal M, Megahed BMH. Chemical composition and biological activity of Physalis peruviana L. Gesunde Pflanz 2019. https://doi.org/10.1007/s10343-019-00456-8.

[21] Elakremi M, Sillero L, Ayed L, Mannal F, Salem R Ben, Labidi J, et al. Chemical composition and biological activity of Pistacia vera L. leaves: Beneficial effects of female leaves extract food products. Cellul Chem Technol 2022;56:309–19.

[22] Farahin AW, Yusoff FM, Basri M, Nagao N, Shariff M. Use of microalgae: Tetraselmis tetrathele extract in formulation of nanoemulsions for cosmeceutical application. J Appl Phycol 2019;31(3):1743–52. https://doi.org/10.1007/s10811-018-1694-9.

[23] Gavra DI, Marian E, Pallag A, Vicaș LG, Lucaciu RL, Micle O, et al. Phytochemical screening and biological activity of ethanolic extract of Rosa X Damascena Mill. Cultivated in the western region of Romania. Farmacia 2022;70(2):248–57. https://doi.org/10.31925/farmacia.2022.2.9.

[24] Ge M, Li Y, Zhu C, Liang G, Jahangir Alam SM, Hu G, et al. Preparation of organic-modified magadiite–magnetic nanocomposite particles as an effective nanohybrid drug carrier material for cancer treatment and its properties of sustained release mechanism by Korsmeyer–Peppas kinetic model. J Mater Sci 2021;56(25):14270–86. https://doi.org/10.1007/s10853-021-06181-w.

[25] Gledovic A, Lezaic AJ, Krstonosic V, Djokovic J, Nikolic I, Bajuk-Bogdanovic D, et al. Low-energy nanoemulsions as carriers for red raspberry seed oil: Formulation approach based on Raman spectroscopy and textural analysis, physicochemical properties, stability and in vitro antioxidant/ biological activity. PloS One 2020;15(4):1–29. https://doi.org/10.1371/journal.pone.0230993.

[26] Hannah K, Maximilian U, Mittag JJ, Julia B, Patrick G, Heiko H. Complex micellization behavior of the polysorbates tween 20 and tween 80. Mol Pharm 2021;18(8):3147–57. https://doi.org/10.1021/acs.molpharmaceut.1c00406.

[27] Ilochonwu BC, Urtti A, Hennink WE, Vermonden T. Intravitreal hydrogels for sustained release of therapeutic proteins. J Control Release 2020;326(April):419–41. https://doi.org/10.1016/j.jconrel.2020.07.031.

[28] Jesumani V, Du H, Pei P, Aslam M, Huang N. Comparative study on skin protection activity of polyphenol-rich extract and polysaccharide-rich extract from Sargassum vachellianum. PloS One 2020;15(1):1–17. https://doi.org/10.1371/journal.pone.0227308.

[29] Jia H, Lian P, Leng X, Han Y, Wang Q, Jia K, et al. Mechanism studies on the application of the mixed cationic/anionic surfactant systems to enhance oil recovery. Fuel 2019;258(September):116–56. https://doi.org/10.1016/j.fuel.2019.116156.

[30] Jiang H, Zhang T, Smits J, Huang X, Maas M, Yin S, et al. Edible high internal phase Pickering emulsion with double-emulsion morphology. Food Hydrocoll 2021;111. https://doi.org/10.1016/j.foodhyd.2020.106405.

[31] Koosha M, Hamedi S. Intelligent chitosan/PVA nanocomposite films containing black carrot anthocyanin and bentonite nanoclays with improved mechanical, thermal and antibacterial properties. Prog Org Coat 2019;127(October 2018): 338–47. https://doi.org/10.1016/j.porgcoat.2018.11.028.
[32] Kumar A, Kaur R, Kumar V, Kumar S, Gehlot R, Aggarwal P. New insights into water-in-oil-in-water (W/O/W) double emulsions: Properties, fabrication, instability mechanism, and food applications. Trends Food Sci Technol 2022;128: 22–37. https://doi.org/10.1016/j.tifs.2022.07.016.
[33] Leibtag S, Peshkovsky A. Cannabis extract nanoemulsions produced by high-intensity ultrasound: Formulation development and scale-up. J Drug Deliv Sci Technol 2020;60(August):101953. https://doi.org/10.1016/j.jddst.2020.101953.
[34] Li J, Ma X, Zhang J, Wang Y, Du M, Xiang Q, et al. Insight into the mechanism of the quality improvement of porcine after ultrasound-assisted immersion freezing. Int J Food Sci Technol 2022;57(8):5068–77. https://doi.org/10.1111/ijfs.15815.
[35] Liang Y, Chen W, Xu W, Sun HG. Distributed order Hausdorff derivative diffusion model to characterize non-Fickian diffusion in porous media. Commun Nonlinear Sci Numer Simul 2019;70(8):384–93. https://doi.org/10.1016/j.cnsns.2018.10.010.
[36] Liu Z, Zhou G, Li S, Wang C, Liu R, Jiang W. Molecular dynamics simulation and experimental characterization of anionic surfactant: Influence on wettability of low-rank coal. Fuel 2020;279(June):118323. https://doi.org/10.1016/j.fuel.2020.118323.
[37] Mahboobian MM, Seyfoddin A, Aboofazeli R, Foroutan SM, Rupenthal ID. Brinzolamide–loaded nanoemulsions: Ex vivo transcorneal permeation, cell viability and ocular irritation tests. Pharm Dev Technol 2019;24(5):600–6. https://doi.org/10.1080/10837450.2018.1547748.
[38] Mashhadian A, Afjoul H, Shamloo A. An integrative method to increase the reliability of conventional double emulsion method. Anal Chim Acta 2022;1197. https://doi.org/10.1016/j.aca.2022.339523.
[39] Matinise N, Kaviyarasu K, Mongwaketsi N, Khamlich S, Kotsedi L, Mayedwa N, et al. Green synthesis of novel zinc iron oxide (ZnFe 2 O 4) nanocomposite via *Moringa Oleifera* natural extract for electrochemical applications. Appl Surf Sci 2018;446:66–73. https://doi.org/10.1016/j.apsusc.2018.02.187.
[40] McClements DJ. Advances in edible nanoemulsions: Digestion, bioavailability, and potential toxicity. Prog Lipid Res 2021;81(October 2020):101081. https://doi.org/10.1016/j.plipres.2020.101081.
[41] Melo RQC, Lia Fook MV, de Lima AGB. Non-fickian moisture transport in vegetable-fiber-reinforced polymer composites using a langmuir-type model. Polymers 2020;12(11):1–18. https://doi.org/10.3390/polym12112503.
[42] Mircioiu C, Voicu V, Anuta V, Tudose A, Celia C, Paolino D, et al. Mathematical modeling of release kinetics from supramolecular drug delivery systems. Pharmaceutics 2019;11(3). https://doi.org/10.3390/pharmaceutics11030140.
[43] Mohammadi-Aloucheh R, Habibi-Yangjeh A, Bayrami A, Latifi-Navid S, Asadi A. Green synthesis of ZnO and ZnO/CuO nanocomposites in Mentha longifolia leaf extract: characterization and their application as anti-bacterial agents. J Mater Sci Mater Electron 2018;29(16):13596–605. https://doi.org/10.1007/s10854-018-9487-0.
[44] Nagaraju PG, Sindhu P, Dubey T, Chinnathambi S, Poornima Priyadarshini CG, Rao PJ. Influence of sodium caseinate, maltodextrin, pectin and their Maillard conjugate on the stability, in vitro release, anti-oxidant property and cell viability of eugenol-olive oil nanoemulsions. Int J Biol Macromol 2021;183:158–70. https://doi.org/10.1016/j.ijbiomac.2021.04.122.
[45] Naghdi S, Sajjadi M, Nasrollahzadeh M, Rhee KY, Sajadi SM, Jaleh B. Cuscuta reflexa leaf extract mediated green synthesis of the Cu nanoparticles on graphene oxide/manganese dioxide nanocomposite and its catalytic activity toward reduction of nitroarenes and organic dyes. J Taiwan Inst Chem Eng 2018;86: 158–73. https://doi.org/10.1016/j.jtice.2017.12.017.
[46] Norizan MN, Moklis MH, Ngah Demon SZ, Halim NA, Samsuri A, Mohamad IS, et al. Carbon nanotubes: Functionalisation and their application in chemical sensors. RSC Adv 2020;10(71):43704–32. https://doi.org/10.1039/d0ra09438b.
[47] Okpala CC. Nanocomposites – an overview. Int J Eng Res Dev 2013;8(11):17–23.
[48] Ozturk B, Parkinson C, Gonzalez-Miquel M. Extraction of polyphenolic antioxidants from orange peel waste using deep eutectic solvents. Sep Purif Technol 2018;206:1–13. https://doi.org/10.1016/j.seppur.2018.05.052.
[49] Padilla-Camberos E, Torres-Gonzalez OR, Sanchez-Hernandez IM, Diaz-Martinez NE, Hernandez-Perez OR, Flores-Fernandez JM. Anti-inflammatory activity of cnidoscolus aconitifolius (Mill.) ethyl acetate extract on croton oil-induced mouse ear edema. Appl Sci (Switz) 2021;11(20). https://doi.org/10.3390/app11209697.
[50] Páez-Hernández G, Mondragón-Cortez P, Espinosa-Andrews H. Developing curcumin nanoemulsions by high-intensity methods: Impact of ultrasonication and microfluidization parameters. Lwt 2019;111(March):291–300. https://doi.org/10.1016/j.lwt.2019.05.012.
[51] Paulo F, Santos L. Microencapsulation of caffeic acid and its release using a w/o/w double emulsion method: Assessment of formulation parameters. Drying Technol 2019;37(8):950–61. https://doi.org/10.1080/07373937.2018.1480493.
[52] Permanadewi I, Kumoro AC, Wardhani DH, Aryanti N. Modelling of controlled drug release in gastrointestinal tract simulation. J Phys Conf Ser 2019;1295(1). https://doi.org/10.1088/1742-6596/1295/1/012063.
[53] Pimentel-Moral S, Ochando-Pulido JM, Segura-Carretero A, Martinez-Ferez A. Stabilization of W/O/W multiple emulsion loaded with Hibiscus sabdariffa extract through protein-polysaccharide complexes. Lwt 2018;90(June 2017):389–95. https://doi.org/10.1016/j.lwt.2017.12.054.
[54] Pongsumpun P, Iwamoto S, Siripatrawan U. Response surface methodology for optimization of cinnamon essential oil nanoemulsion with improved stability and antifungal activity. Ultrason Sonochem 2020;60(May 2019):104604. https://doi.org/10.1016/j.ultsonch.2019.05.021.
[55] Rafińska K, Pomastowski P, Rudnicka J, Krakowska A, Maruśka A, Narkute M, et al. Effect of solvent and extraction technique on composition and biological activity of Lepidium sativum extracts. Food Chem 2019;289(March):16–25. https://doi.org/10.1016/j.foodchem.2019.03.025.
[56] Rehman A, Tong Q, Jafari SM, Assadpour E, Shehzad Q, Aadil RM, et al. Carotenoid-loaded nanocarriers: A comprehensive review. Adv Colloid Interface Sci 2020;275:102048. https://doi.org/10.1016/j.cis.2019.102048.
[57] Robert P, Zamorano M, González E, Silva-Weiss A, Cofrades S, Giménez B. Double emulsions with olive leaves extract as fat replacers in meat systems with high oxidative stability. Food Res Int 2019;120(November):904–12. https://doi.org/10.1016/j.foodres.2018.12.014.
[58] Safna MI, Visakh UV, Gangadharan A. Biological activity of hexane extract of Hemigraphis colorata, an indigenous wound healing plant. Mater Today Proc 2019;25:294–7. https://doi.org/10.1016/j.matpr.2020.01.461.
[59] Sagar NA, Pareek S, Sharma S, Yahia EM, Lobo MG. Fruit and vegetable waste: Bioactive compounds, their extraction, and possible utilization. Compr Rev Food Sci Food Saf 2018;17(3):512–31. https://doi.org/10.1111/1541-4337.12330.
[60] Saidi M, Dabbaghi A, Rahmani S. Swelling and drug delivery kinetics of click-synthesized hydrogels based on various combinations of PEG and star-shaped PCL: Influence of network parameters on swelling and release behavior. Polym Bull 2020;77(8):3989–4010. https://doi.org/10.1007/s00289-019-02948-z.
[61] Saini A, Panesar PS, Bera MB. Valorization of fruits and vegetables waste through green extraction of bioactive compounds and their nanoemulsions-based delivery system. Bioresour Bioprocess 2019;6(1). https://doi.org/10.1186/s40643-019-0261-9.
[62] Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (review). Int J Oncol 2019;54(2):407–19. https://doi.org/10.3892/ijo.2018.4661.
[63] Siddik MAB, Shin AC. Recent progress on branched-chain amino acids in obesity, diabetes, and beyond. Endocrinol Metab 2019;34(3):234–46. https://doi.org/10.3803/EnM.2019.34.3.234.
[64] Silva M, Chandrapala J. Ultrasonic emulsification of milk proteins stabilized primary and double emulsions: A review. Food Rev Intl 2021;00(00):1–23. https://doi.org/10.1080/87559129.2021.1934006.
[65] Sun B, Hu Y, Cheng H, Tao S. Releases of brominated flame retardants (BFRs) from microplastics in aqueous medium: Kinetics and molecular-size dependence of diffusion. Water Res 2019;151:215–25. https://doi.org/10.1016/j.watres.2018.12.017.
[66] Takakura A, Beppu K, Nishihara T, Fukui A, Kozeki T, Namazu T, et al. Strength of carbon nanotubes depends on their chemical structures. Nat Commun 2019;10(1): 1–7. https://doi.org/10.1038/s41467-019-10959-7.
[67] Tanase C, Cosarcă S, Muntean DL. A critical review of phenolic compounds extracted from the bark of woody vascular plants and their potential biological activity. Molecules 2019;24(6). https://doi.org/10.3390/molecules24061182.
[68] van Breda, de Kok. Smart combinations of bioactive compounds in fruits and vegetables may guide new strategies for personalized prevention of chronic diseases. Mol Nutr Food Res 2018;62(1):1–12. https://doi.org/10.1002/mnfr.201700597.
[69] Vasantha-Rupasinghe HP. Special issue "flavonoids and their disease prevention and treatment potential": Recent advances and future perspectives. Molecules 2020;25(4746):1–7.
[70] Vater C, Adamovic A, Ruttensteiner L, Steiner K, Tajpara P, Klang V, et al. Cytotoxicity of lecithin-based nanoemulsions on human skin cells and ex vivo skin permeation: Comparison to conventional surfactant types. Int J Pharm 2019;566 (March):383–90. https://doi.org/10.1016/j.ijpharm.2019.05.078.
[71] Vinatoru M, Mason TJ, Calinescu I. Ultrasonically assisted extraction (UAE) and microwave assisted extraction (MAE) of functional compounds from plant materials. TrAC - Trends Anal Chem 2017;97:159–78. https://doi.org/10.1016/j.trac.2017.09.002.
[72] Walia N, Chen L. Pea protein based vitamin D nanoemulsions: Fabrication, stability and in vitro study using Caco-2 cells. Food Chem 2020;305(April 2019):125475. https://doi.org/10.1016/j.foodchem.2019.125475.
[73] Wen L, Zhang Z, Sun DW, Sivagnanam SP, Tiwari BK. Combination of emerging technologies for the extraction of bioactive compounds. Crit Rev Food Sci Nutr 2020;60(11):1826–41. https://doi.org/10.1080/10408398.2019.1602823.
[74] Xia Z, Han Y, Du H, McClements DJ, Tang Z, Xiao H. Exploring the effects of carrier oil type on in vitro bioavailability of β-carotene: A cell culture study of carotenoid-enriched nanoemulsions. Lwt 2020;134(June):110224. https://doi.org/10.1016/j.lwt.2020.110224.
[75] Xiang J, Apea-Bah FB, Ndolo VU, Katundu MC, Beta T. Profile of phenolic compounds and antioxidant activity of finger millet varieties. Food Chem 2019; 275:361–8. https://doi.org/10.1016/j.foodchem.2018.09.120.
[76] Xu D, Zheng B, Che Y, Liu G, Yuan Y, Wang S, et al. The stability, microstructure, and microrheological properties of Monascus pigment double emulsions stabilized by polyglycerol polyricinoleate and soybean protein isolate. Front Nutr 2020;7 (December):1–13. https://doi.org/10.3389/fnut.2020.543421.
[77] Xu LQ, Neoh KG, Kang ET. Natural polyphenols as versatile platforms for material engineering and surface functionalization. Prog Polym Sci 2018;87:165–96. https://doi.org/10.1016/j.progpolymsci.2018.08.005.
[78] Yildiz G, Izli G. The effect of ultrasound pretreatment on quality attributes of freeze-dried quince slices: physical properties and bioactive compounds. J Food Process Eng 2019;42(5):1–8. https://doi.org/10.1111/jfpe.13223.
[79] Yourdkhani M, Leme-Kraus AA, Aydin B, Bedran-Russo AK, White SR. Encapsulation of grape seed extract in polylactide microcapsules for sustained

bioactivity and time-dependent release in dental material applications. Dent Mater 2017;33(6):630–6. https://doi.org/10.1016/j.dental.2017.03.009.

[80] Zannella C, Giugliano R, Chianese A, Buonocore C, Vitale GA, Sanna G, et al. Antiviral activity of vitis vinifera leaf extract against sars-cov-2 and hsv-1. Viruses 2021;13(7). https://doi.org/10.3390/v13071263.

[81] Zhang H, Chen G, Liu M, Mei X, Yu Q, Kan J. Effects of multi-frequency ultrasound on physicochemical properties, structural characteristics of gluten protein and the quality of noodle. Ultrason Sonochem 2020;67(April):105135. https://doi.org/10.1016/j.ultsonch.2020.105135.

[82] Zhu D, Qiao M, Liu J, Tao T, Guo C. Engineering pristine 2D metal-organic framework nanosheets for electrocatalysis. J Mater Chem A 2020;8(17):8143–70. https://doi.org/10.1039/d0ta03138k.

[83] Zidane A, Firoozabadi A. Fickian diffusion in CO2 injection: A two-phase compositional flow model with fully 3D unstructured gridding. Fuel 2021;303 (April):121278. https://doi.org/10.1016/j.fuel.2021.121278.