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REVIEW ARTICLE

Health properties of bioactive food compounds-loaded micro and nano-encapsulation systems: A review

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Abstract

Bioactive food compounds (BFCs) are micronutrients existing in small quantities in various foods. Plant, microbes, and animals are considered the main sources of bioactive components including polyphenols, flavonoids, ω-3 FAs, and so on. BFCs have many biological functions such as antioxidant, antidiabetic, antiobesity, anti-cardiovascular, anticancer, anti-inflammatory, antimicrobial, immune-modulatory, cholesterol reduction characteristics, and others. However, incorporation of BFCs in food or pharmaceutical formulations is limited because of their high liability against temperature, pH, shear, pressures, and light, as well as poor hydro-solubility in some of these compounds, low stability under human gastrointestinal conditions, and thereby lower bioavailability (BA) and reducing functional activity. Therefore, encapsulation of BFCs using micro/nanostructure systems can overcome these challenges. These encapsulation systems include nano-silver, nano-gold, nano-emulsions, liposomes, cubosomes, biopolymer-based nanoparticles, nano-gels, and so on. Finally, biopolymer-based nanoparticles and nano-gels are good choices to encapsulate the BFCs compared to other available encapsulation systems due to their advantages. Furthermore, encapsulation of BFCs in micro/nano-systems improved their bio-efficacy including antioxidant, antidiabetic, antiobesity, anti-cardiovascular, anticancer, anti-inflammatory, antimicrobial, and immune-modulatory. Among all encapsulated-BFCs, encapsulated-curcumin and -quercetin showed the highest bio-efficacy. However, further studies regarding stability, BA, and *in vivo* work of BFCs-loaded micro/nano-encapsulation systems are recommended to evaluate the therapeutic efficacy including physicochemical stability, target mechanisms, cellular internalization, and release kinetics.

Keywords: Bioactive food compounds; Bioavailability; Encapsulation systems; Health properties; Stability.

1. Introduction

In recent years, multiple diseases are increasing day by day especially those that are related to diet such as diabetes, obesity, cardiovascular, cancer, etc. Therefore, the consumption of healthy foods that are rich in bioactive compounds is an important issue for improving human health (Silva *et al.*, 2019; Wei *et al.*, 2012; Ahmad and Gani, 2021; Rashwan *et al.*, 2022b). Bioactive food compounds (BFCs) are micronutrients existing in small quantities in various foods, which may provide human health promotion against chronic disease. Scientific literature reported that BFCs have many biological functions such as antioxidant, antidiabetic, antiobesity, anti-cardiovascular, anticancer, anti-inflammatory, antimicrobial, immune-modulatory, and cholesterol reduction effects, etc. (Silva *et al.*, 2019; Mukhtar *et al.*, 2020; Varela-López *et al.*, 2015; Karim *et al.*, 2021). However, incorporation of bioactive compounds and bioactive compounds-rich foods in food or pharmaceutical formulations is limited due to their high liability against

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operational parameters (e.g., temperature, pH, shear, pressures, light, etc.), poor hydro-solubility in some of these compounds, and low stability under human gastrointestinal conditions, and thereby lower bioavailability and reducing functional activity (Nurhadi *et al.*, 2020; Wang *et al.*, 2020; Mar *et al.*, 2020a; Katariya, Arya and Pandit, 2020; Rashwan *et al.*, 2022b). Besides, some consumers do not accept taking some BFCs (i.e., saponins, tannins, geosmin, and pyrazine derivatives) orally due to their unfavorable flavor (Bao *et al.*, 2019; Wang *et al.*, 2020). Therefore, the incorporation of BFCs in micro/nanostructures can overcome these challenges, and several variations can be used to achieve this goal, highlighting the micro/nanoencapsulation (Pan and Nitin, 2015; Rehman *et al.*, 2019; Choi *et al.*, 2020; Peanparkdee, Yamauchi and Iwamoto, 2018).

Nowadays, in the food and pharmaceutical industry, there is an increasing demand for encapsulation systems to provide protection of active compounds from uncoverable conditions, deliver them under specific conditions, and enhance their biological activity (Bourbon, Cerqueira and Vicente, 2016; Rashwan *et al.*, 2021a). Micro- and nano-encapsulation systems are coating techniques for core material (solid, liquid, gas) using encapsulation materials (bio and/or non-biomaterials). Recent developments from these techniques have been used for encapsulating BFCs to fortify and improve their functionalities in food products, hence, enhancing and protecting their health benefits (Pool *et al.*, 2013; Wang *et al.*, 2020; Fang *et al.*, 2020). Despite the great development of different types of micro/nano-encapsulation systems such as nano-silver, nano-gold, nano-emulsions, liposomes, cubosomes, biopolymer-based nanoparticles, etc. choosing the suitable encapsulation system especially that produced from biomaterials is a very important issue. Safety, ingredients, sizes, shapes, surface charge, stability, and the different mechanisms of targeted delivery are playing an important role in choosing suitable encapsulation systems (de Almeida Paula *et al.*, 2018; Fidan-Yardimci *et al.*, 2019; Radbeh *et al.*, 2020; Bourbon, Cerqueira and Vicente, 2016; Clayton *et al.*, 2009; Mohsen *et al.*, 2021). Overall, our manuscript gives information about the stability of non-encapsulated and encapsulated BFCs, besides, the bioavailability (BA) of these components. Furthermore, it gives some examples of encapsulation systems that can enhance the stability and BA of BFCs. Additionally, explores and discusses comprehensively the biological activity of encapsulated-bioactive compounds for giving a clear understanding to the readers, hence, providing some new opinions for thinking about future research scopes.

2. Stability of non-encapsulated and encapsulated-bioactive compounds

Generally, BFCs can be categorized into three groups based on their source, ionization mode, and solubility as presented in **Fig. 1** (Hamzalıoğlu and Gökmen, 2016; Pool *et al.*, 2013; Meng *et al.*, 2020; Silva *et al.*, 2019; Mazzoli, Riedel and Pessione, 2017; Pubchem, 2021; Sathiyaseelan *et al.*, 2020). Bioactive compounds are available in many foods as shown in **Table 1a, and 1b**. Besides, BFCs have characterized by a wide color range (light-yellow to black), and these colors are considered an important indicator of food quality. Hence, the loss of food colors indicates degrading bioactive components in this food. In the last tenth decades, many researchers investigated factors affecting the stability of bioactive compounds, which also affect the biological activity of these components (Zupancic, Lavric and Kristl, 2015; Wang *et al.*, 2020; Lee *et al.*, 2020). For example, α-carotene, β-carotene, tocopherols, and tocotrienols in red palm oil have degraded with an increase in storage temperature and time, therefore, the L* (lightness) value has risen, whereas the a*((+) red/ (−) green), b* ((+) yellow/ (−) blue), and C (chroma) values significantly reduced (Lee et al., 2020). Further, high temperature has a negative effect on trans-RSV stability (Zupancic, Lavric and Kristl, 2015). At pH 7.4 trans-RSV rapidly degraded at 25 and 37°C, while the degradation was slowed at 4°C and prevented at −22°C (Zupancic, Lavric and Kristl, 2015). Thermal treatment during the preparation of beet-rots jam significantly reduced total phenolics (13.8%), betalains (56.3%), and antioxidant capacity (13.2–28.2%), but significantly increased total flavonoids (99.3%) (Wang et al., 2020). At pH 1.2, the half-life of trans-resveratrol (trans-RSV) was 329 days, while the half-life of trans-RSV was decreased to 3.3 min at pH 10. Besides, trans-RSV in buffer with pH 9.0 and pH 10.0 was completely degraded

during less than 24 and 9 min, respectively. These results indicated that *trans*-RSV only had stability under acidic conditions, while *trans*-RSV exponentially degraded when the pH became alkaline (Zupancic, Lavric and Kristl, 2015).

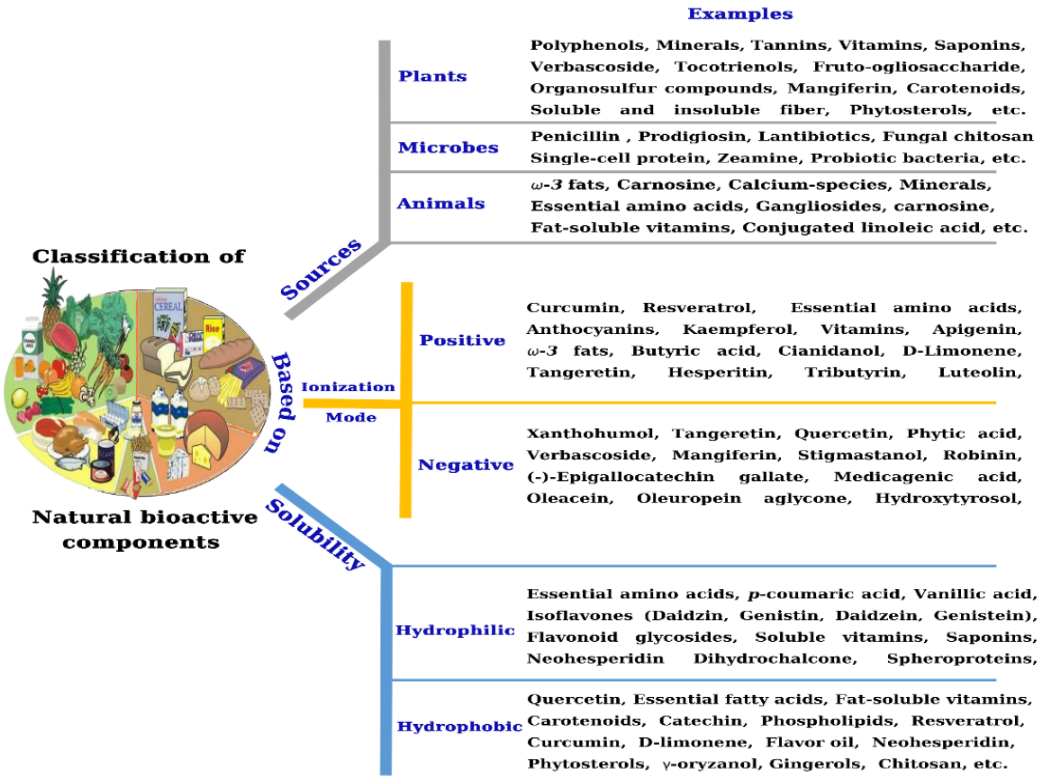

Fig. 1. Classification of bioactive food components based on sources, ionization mode, and solubility.

Table 1a. The occurrence in foods, solubility, and extraction solvents of some flavonoid compounds

Bioactive compounds	Occurrence in foods	Solubility	Extraction solvents	References
Silymarin	Milk thistle (*Silybum Marianum*)	Poor water solubility	Ethanol, methanol, acetonitrile, and acetone	(Mukhtar *et al.*, 2020; El-Samaligy, Afifi and Mahmoud, 2006)
Luteolin	Broccoli, green pepper, parsley, oregano, carrots, and rosemary	Poor water solubility	Methanol, ethanol, chloroform, and dichloromethane	(Hamzalıoğlu and Gökmen, 2016; Ramešová *et al.*, 2012)
Apigenin	Parsley, celery, onions, oranges, chamomile, thyme, oregano, basil, tea, beer, and wine	Quite low aqueous solubility	Tetrahydrofuran	(Zhai *et al.*, 2013; Brad and Zhang, 2018; Salehi *et al.*, 2019b)
Tangeretin	Tangerine and other citrus peels	Insoluble in water	1-ethyl-3-methylimidazolium methylphosphonate	(Mizuno, Yoshikawa and Usuki, 2019)
Quercetin	Onions, grapes, berries, cherries, broccoli, and citrus fruits	Poor water solubility	Deep eutectic solvents	(Pinheiro *et al.*, 2020; Qi *et al.*, 2020; Ramešová *et al.*, 2012; Wang *et al.*, 2019a; Ciardi *et al.*, 2021)
Kaempferol	Spinach and kale, and herbs such as dill, chives, and tarragon	Insoluble in water	Methanol or ethanol	(Cid-Ortega and Monroy-Rivera, 2018; Dabeek and Marra, 2019)

(Continue Table 1a)

Bioactive compounds	Occurrence in foods	Solubility	Extraction solvents	References
Myricetin	Cranberry, dock, sweet potato leaves, rutabagas, garlic, blueberry, and blackberry	Insoluble in water	Methanol–ascorbic acid–hydrochloric acid	(Taheri *et al.*, 2020; Franklin and Myrdal, 2015; Ozcan and Yaman, 2015)
Galangin	Honey and Alpinia officinarum Hance (*Zingiberaceae*)	Slightly water-soluble	The mixer of water, methanol, and ethanol	(Sabry *et al.*, 2021; Zhu *et al.*, 2018)
Hesperidin	Lemons, sweet oranges, and blood orange	Very poorly soluble in water	Methanol and ethanol	(Majumdar and Srirangam, 2009; Karim *et al.*, 2021)
Naringenin	Grapefruits, sour orange, tart cherries, tomatoes, Greek oregano	Poor water solubility	Ethanol and water mixture	(Zhang *et al.*, 2013)
Pelargonidin	Berries fruits, plums, and pomegranates	Water-soluble	Acidified organic solvents-water	(Shishir *et al.*, 2020; Rashwan *et al.*, 2021a)
Isorhamnetin	Pears, olive oil, wine, and tomato sauce	Insoluble in water	Methanol, tetrahydrofuran, and isopropanol	(Varela-López *et al.*, 2015; Wang *et al.*, 2005)
Taxifolin	Onions, French maritime bark, tamarind seeds, and milk thistle	Slightly soluble in water	50% ethanol	(Das *et al.*, 2021; Wu *et al.*, 2017)

Table 1b. The component family, occurrence in foods, solubility, and extraction solvents of some other bioactive compounds

Bioactive compounds	Component family	Occurrence in foods	Solubility	Extraction solvents	References
β-Carotene	Terpenoids (isoprenoids)	Carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, and cantaloupe	Insoluble in water	The mixture of acetone and hexane	(Bao *et al.*, 2019; Tan *et al.*, 2014)
Proanthocyanidins	Polyphenols	Cranberry, blueberry, grape seeds, and *Melastoma dodecandrum* Lour fruit.	Water-soluble	The mixture of acetone and water	(Sorour *et al.*, 2017; Rashwan *et al.*, 2022a; Rashwan *et al.*, 2021a; Zineb *et al.*, 2022)
Curcumin	Polyphenols	Turmeric (*Curcuma longa*)	Insoluble in water	Ethanol	(Pontes-Quero *et al.*, 2020; Meng *et al.*, 2021; Rashwan *et al.*, 2022b)
Saponins	Glycosides	Soapwort (*Saponaria officinalis* L.), asparagus, beans, blackberries, peas, potatoes, sugar beet, and tea	Water-soluble	The mixture of ethanol and water (20%)	(Akbal *et al.*, 2018; Cheok, Salman and Sulaiman, 2014)
Resveratrol	Polyphenols (Stilbenoid)	Grapes, wine, grape juice, peanuts, cocoa, and berries	Poor aqueous solubility	95 % ethanol	(Jayan *et al.*, 2019; Zupancic, Lavric and Kristl, 2015)
Tributyrin	Fat (A triester of butyric acid and glycerol)	Butter and almond	Insoluble in water	Chloroform-methanol (2:1 v/v)	(Li *et al.*, 2021; Sanguansri *et al.*, 2013)

(Continue Table 1b)

Bioactive compounds	Component family	Occurrence in foods	Solubility	Extraction solvents	References
Eicosapentaenoic acid (EPA)	Omega-*3* fatty acids (ω-3 FAs)	Cold-water fatty fish, including salmon, tuna, mackerel, sardines, shellfish, and herring	Insoluble in water	Hexane (n-hexane: isopropanol (2:3) and 2-butanol) and ethanol	(Gu, Kavanagh and McClure, 2021)
Docosahexaenoic acid (DHA)	ω-3 FAs	Cold-water fatty fish, including salmon, tuna, mackerel, sardines, shellfish, herring, and *Crypthecodinium cohnii*	Insoluble in water	Hexane (n-hexane: isopropanol (2:3) and 2-butanol) and ethanol	(Calder, 2016; Stramarkou *et al.*, 2021)
Mangiferin	Polyphenols	*Mangifera indica*, Iris unguicularis, and honey bush	Sparingly soluble in water	50% aqueous ethanol	(Varela-López *et al.*, 2015; Khurana *et al.*, 2016)
Thymoquinone	Monoterpenoid class benzoquinone	Black seeds of *Nigella sativa* L. (black cumin)	Sparingly soluble in water	Ethanol and methanol	(Varela-López *et al.*, 2015; Goyal *et al.*, 2017; Tabassum *et al.*, 2021)
Hyperforin	-	St. John's-worts (Hypericaceae)	Sparingly soluble in water	The mixture of 50:50 v/v ethanol-methanol	(Alali and Tawaha, 2009; Gaid *et al.*, 2018)
Hypericin	-	Yellow flower of Hypericum perforatum (St. John's wort)	Non-soluble in water	The mixture of ethanol: acetone 2:1 v/v	(Alali and Tawaha, 2009; Ramezani and Zamani, 2017)
Capsaicin	Alkaloid compound	Jalapeño peppers, cayenne peppers, and other chili peppers	Insoluble in water	Hexane, chloroform, and ethanol	(Arunprasert *et al.*, 2022; Merritt *et al.*, 2022)
N-Acetylcysteine	Thiol mucolytic compound	Chicken, turkey, yogurt, cheese, eggs, sunflower seeds, and legumes	Soluble in water	-	(Wang *et al.*, 2022)
Coenzyme Q10	Vitamin-like substance	Oily fish (e.g., salmon and tuna), organ meats (liver), and whole grains	High water solubility	Methanol: hexane (85:15, v/v) in the presence of surfactant Tween-20 at 3% and polypropylene tubes	(Cheng *et al.*, 2021; Mohsen *et al.*, 2021)

Besides, vitamin B12 activity in the milk was destroyed by approximately 50% upon heat sterilization of milk, as well as exposure of the milk to sunlight also caused a progressive loss of vitamin B12 (Ford, 1967). This loss of folic acid occurred due to the oxidative destruction of the milk's ascorbic acid. Additionally, the oxygen tension in the milk assisted in the decreased stability of vitamin B6, thiamine, nicotinic acid, riboflavin, and biotin during the heating process and exposure to sunlight. Therefore, milk vitamins can largely be preserved via the thorough exclusion of oxygen from the milk during heat processing and subsequent storage (Ford, 1967). The exposition of BFCs to oxygen also destroys their stability and bio-efficacy. The exposition of natural flavonoid compounds such as quercetin and luteolin to atmospheric oxygen led to degradation and complicates their analytical determinations (Ramešová *et al.*, 2012).

Thus, the stability of bioactive compounds can be improved by incorporating them into

encapsulation systems. In the food and most of the pharmaceutical industry, suitable encapsulation systems can be prepared and produced from biomaterials (biopolymers) such as lipids, proteins, polysaccharides, etc. (**Fig. 2**) (Mohammadian *et al.*, 2020; Akbari-Alavijeh, Shaddel and Jafari, 2020; Shishir *et al.*, 2020). These encapsulation systems include micro/nanoemulsions, liposomes, niosomes, solid lipid nanoparticles, biopolymer nanoparticles, microgels, etc. (**Fig. 3**) (Jalali-Jivan, Garavand and Jafari, 2020; Rashwan *et al.*, 2021a). For instance, the UVC radiation exposure test showed that encapsulation of indole-*3*-carbinol (I3C) in nanocapsules (NCs) suspension protected the I3C from degradation during 2 h compared to free-I3C (Gehrcke *et al.*, 2018). Furthermore, pelargonidin-*3*-O-glucoside-encapsulated in pectin-chitosan-nanoliposome (P3G-P-CH-NL) demonstrated high stability against the degradation by thermal and food simulant, besides, *in vitro* study showed the improvement of P3G retention after being loaded in P-CH-NL (Shishir *et al.*, 2020). Additionally, photo-stability experiments showed an increase in photostability of curcumin-(Cur) loaded in poly lactic-co-glycolic acid nanoparticles (Cur-PLGN) by approximately ~22 % compared to non-encapsulated-Cur. Solubility studies also revealed that Cur-solubility increased by ~13-fold after being loaded in poly lactic-co-glycolic acid nanoparticles (Kumari *et al.*, 2020). Cur-encapsulated in complex nanoparticles was more stable when exposed to ultraviolet light. In which, the half-life ($t_{1/2}$) values manifested that Cur-encapsulated in carboxymethyl dextrin (CMD), and Cur-encapsulated in zein nanoparticles had a higher photostability than non-encapsulated Cur (Meng *et al.*, 2021). This is probably due to hydrogen bond formation between Cur and CMD molecules as well as the presence of the double bonds and aromatic amino acid residues in zein assisted to enhance the stability of Cur (Meng *et al.*, 2021; Mangolim *et al.*, 2014). Furthermore, the Cur $t_{1/2}$ value was further increased when it was encapsulated in zein/CMD nanoparticles. This might be ascribed to the formation of a CMD layer that provided a stronger physical barrier. On the other hand, Encapsulated Cur showed higher thermal stability than free Cur after thermal treatment at different temperatures (75 °C, 85 °C, and 95 °C, respectively). This may have occurred because the active group of Cur was protected in the hydrophobic cavity of CMD and zein (Meng *et al.*, 2021). Additionally, incorporating Coenzyme-Q10 (Co-Q10) niosomes coated by PEG and chitosan increased its photo-stability, heat stability, and storage stability (Cheng *et al.*, 2021).

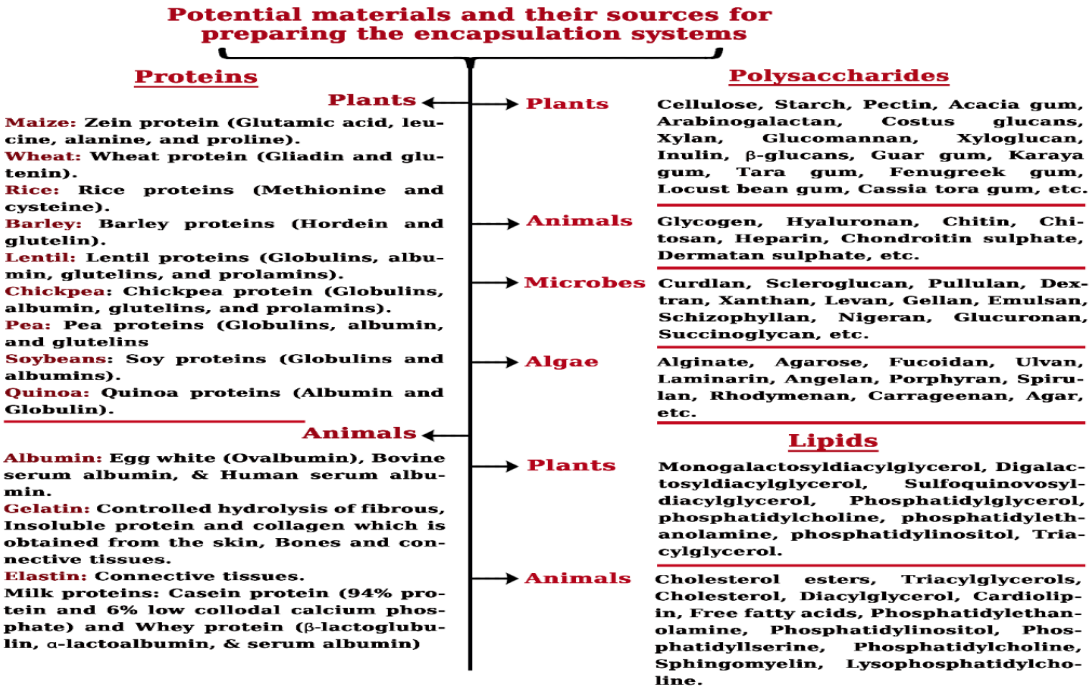

Fig. 2. Potential materials and their sources for preparing the encapsulation systems

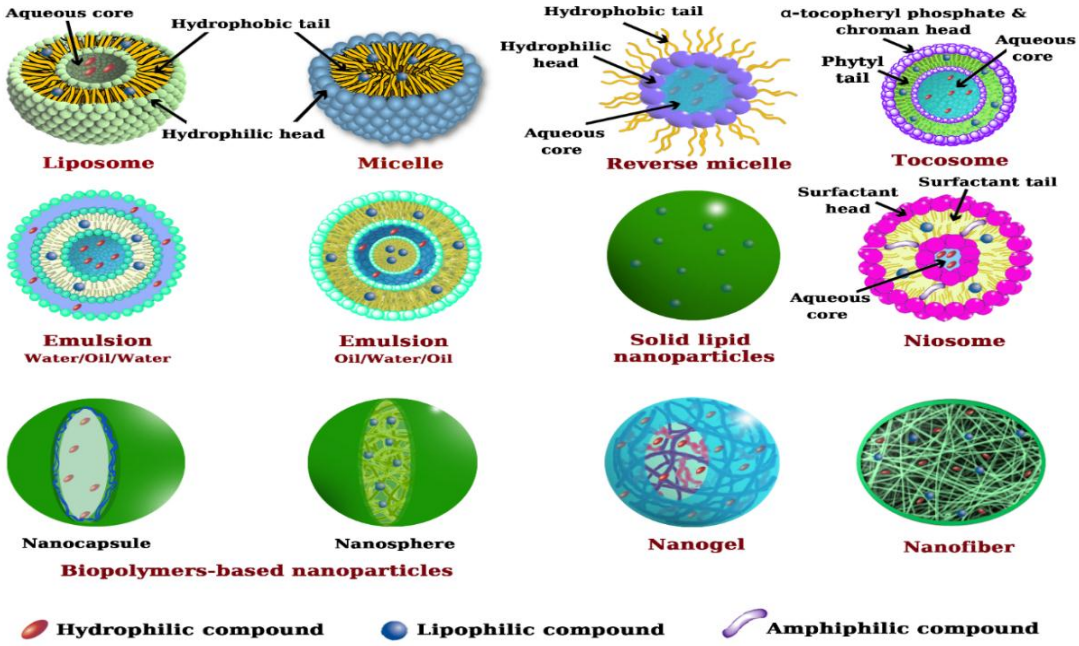

Fig. 3. Schematic picture of the potential encapsulation systems for improving the stability and bioavailability of bioactive food compounds.

3. Bioavailability of encapsulated-bioactive compounds

Bioavailability (BA) of bioactive components that enter our bodies is a very important issue for utilizing the health benefit of these components. BA is considered a key step in ensuring the efficacy of both natural (bioactive compounds) and synthetic drugs. It is a complex process involving four phases, liberation, absorption, distribution, metabolism, and elimination (Rein *et al.*, 2013). Many natural bioactive components have low oral BA due to their low solubility as well as low stability in gastrointestinal (GI) fluid and their poor absorption through the intestinal epithelial layer. Therefore, lately, researchers have tried to improve the BA of bioactive ingredients via incorporating them in encapsulation systems e.g., micro/nanoemulsions, solid lipid nanoparticles, biopolymer nanoparticles, microgels, and so on (Dima *et al.*, 2020; Casadey *et al.*, 2020). Suitable encapsulation systems can easily enter the human body as well as enhance the stability, BA, absorption, and cellular uptake of bioactive compounds. Furthermore, it provides site-specific drug delivery, stimuli-responsive release, and controlled release (Rizvi and Saleh, 2018; Akbari-Alavijeh, Shaddel and Jafari, 2020; Rostamabadi *et al.*, 2021; Mar *et al.*, 2020b; Casadey *et al.*, 2020).

For example, pharmacokinetics and biodistribution studies found that modified stealth nanoparticles (Tf-PEG-NP) encapsulating poly(ethylene) glycol-hydroxycamptothecin conjugate (PEG-HCPT) as anti-tumor showed the lengthiest retention time in the blood (8.94-fold that of PEG-HCPT), the highest tumor accumulation (9.03-fold, 3.11-fold that of PEG-HCPT and HCPT-loaded counterpart, respectively) (Hong *et al.*, 2010). In *in vitro* drug release study, nearly 84% of apigenin was released from polymeric micelles within 36 h, showing the sustained-release property (Zhai *et al.*, 2013). Encapsulation of Cur in complexation of chitosan with alginate assisted to reduce Cur loss by 20% and led to extending the mean release time by 40 min in simulated gastric fluid (Akolade, Oloyede and Onyenekwe, 2017). The incorporation of bilberry extract into citrus pectin (biopolymer nanoparticles) enhanced intestinal accessibility during passage through the small intestine and modulated formation of degradation product phloroglucinol aldehyde in human plasma (Mueller *et al.*, 2018). Moreover, the bioavailability of ANCs can be modified in the

short-term using whey protein encapsulation (Mueller *et al.,* 2018). Encapsulation of Cur in zein nanoparticles that have a stabilized dual coating shell structure in combination with sodium caseinate and sodium alginate is effective for improving the water solubility of Cur, significantly improved its photochemical stability, and provided controlled release under simulated gastrointestinal conditions (Liu *et al.,* 2019). *In vitro* release experiments have shown that poly lactic-co-glycolic acid nanoparticles were able to release ~45% of their cargo (Cur) in 8 h (Kumari *et al.,* 2020). In addition, encapsulation of Cur in zein/CMD nanoparticles significantly delayed the release of Cur in simulated gastrointestinal fluids (Meng *et al.,* 2021).

Additionally, *in vitro* study showed that liposomal formulation enhanced the bioaccessibility and stability of black mulberry waste extract (i.e., anthocyanins) under high temperature and pH compared to free extract (Gültekin-Özgüven *et al.,* 2016). Liposome-loaded galangin significantly promotes oral absorption and raised the extent of galangin release *in vitro* as well as its oral bioavailability (470.12%) *in vivo* (Zhu *et al.,* 2018). This may be because the encapsulation of galangin in liposomes greatly increased its solubility, which could improve its bioavailability. In which, within the lipid bilayer of a liposome, the hydroxyl group of cholesterol could bond with the aqueous environment. Hence, these interactions would influence the release rate of galangin. The multi-layer structure of liposomes probably caused the biphasic pattern of drug release. The drug wrapped in the inner layer may take a longer time to leak out than the drug wrapped in the outer layer which released at a faster rate (Zhu *et al.,* 2018). Encapsulation of anthocyanins (ANCs) in niosome also increased their bioavailability, further, niosome system improved the release time to 10 h for ANCs (Fidan-Yardimci *et al.,* 2019). FTIR and DSC analysis for tannic acid-loaded niosomes confirmed that the absence of drug-excipient interactions, as well as *in vitro* release of tannic acid-loaded niosomes showed a controlled release profile. In which, tannic acid encapsulated revealed a slow and controlled inhibition of bacterial growth for 72 h compared to the free tannic acid that was used up in the first hours in the time-kill assay (Heidari *et al.,* 2020). Moreover, galangin-loaded niosomes showed a significantly higher release rate than the aqueous suspension of the drug after 48 h (Sabry *et al.,* 2021). Further, incorporating Co-Q10 niosomes coated by PEG and chitosan exhibited excellent sustained release effects (Cheng *et al.,* 2021).

The dialysis bag technique showed that approximately 100% of indole-3-carbinol (I3C) was released from nanocapsules (NCs) at 360 min (Gehrcke *et al.,* 2018). Encapsulation of *trans*-RSV into nanofiber enhanced its release, whereas most of the *trans*-RSV was released in the first 4 h and the remainder in the following 8 h in a sustained manner (Zupancic, Lavric and Kristl, 2015). Additionally, *in vitro* release assay also revealed that most oregano essential oil-loaded chitosan/poly(ε-caprolactone) hybrid nanofibrous mats remained (56.4–81.7%) after 96 h, demonstrating its durability (Hasanpour Ardekani-Zadeh and Hosseini, 2019). Furthermore, *in vitro* results showed that quercetin-loaded selenium nanoparticles (Que-SeNPs) coated with acacia and polysorbate 80 (P80) (nanocomposites) (P80-Que-SeNCs) had high aqueous solubility compared to free quercetin (Qi *et al.,* 2020).

4. Health properties of encapsulated-bioactive compounds

Biological activity describes the beneficial or adverse effects of a drug on living matter. Pharmacological studies showed that BFCs have several biological activities including antioxidant, antidiabetic, antimicrobial, antifungal, anticancer, etc. (**Table 2**). Therefore, encapsulation of BFCs in micro/nanoparticles can improve their bioavailability, enhancing their health properties (Nikolic *et al.,* 2020; Liu *et al.,* 2019; Akbal *et al.,* 2018; Ahmad and Gani, 2021). In the next section, we explored the biological activities of encapsulated/loaded-bioactive compounds in different encapsulation systems.

4.1. Antioxidant activity

Bioactive compounds are well known it having a great antioxidant activity that can eliminate reactive oxygen species (**Table 2**). Thus, the incorporation of these components in various encapsulation systems can enhance their antioxidant capacity (Trinh *et al.,* 2019; Fonseca *et al.,* 2019; Tan *et al.,* 2014; Meng *et al.,* 2021; Ahmad and Gani, 2021). Encapsulation of

carotenoids in liposomes enhanced their antioxidant activity through the antioxidant models, including DPPH (1, 1-diphenyl-2-picrylhydrazyl free radical), FRAP (ferric reducing antioxidant power), and lipid peroxidation inhibition capacity. Furthermore, liposome-encapsulation of lutein and β-carotene not only inhibited the lipid peroxidation but also protected them against pro-oxidation elements (Tan *et al.*, 2014). *Trachyspermum copticum* essential oil encapsulated in niosome showed an excellent antioxidant activity (IC_{50} of 18.32 µg/ml) (Trinh *et al.*, 2019). Cur-loaded nanoemulsion exhibited very fast activity, neutralizing the free radical in the first 5 min upon starting the reaction, even though encapsulation is expected to provide extended activity (Nikolic *et al.*, 2020). Moreover, the incorporation of Cur with zein nanoparticles showed more effectiveness in scavenging the DPPH compared to vitamin C (Liu *et al.*, 2019). CMD-Cur complex, zein-Cur nanoparticles, and zein/CMD-Cur nanoparticles showed higher DPPH scavenging abilities than free Cur in water, which were 61.49%, 55%, 68.25%, 19.56%, respectively (Meng *et al.*, 2021). This is attributed to the fact that the hydrophobic Cur-encapsulated in the nanoparticles or CMD with the hydrophilic surface was better dispersed in water, causing to increase in the contact between Cur and free radicals (Meng *et al.*, 2021; Liang *et al.*, 2015). Additionally, Cur-loaded in zein/CMD nanoparticles exhibited stronger scavenging ability than CMD-Cur complex and zein-Cur nanoparticles. A possible explanation for this result was that the complex of CMD and zein made the conjugated diene structure of Cur easier to provide protons to DPPH and improve the free radical scavenging ability of Cur (Meng *et al.*, 2021; Liang *et al.*, 2015). $ABTS^{\bullet+}$ radical elimination method showed that the 40% carvacrol-loaded starch electrospun nanofibers exhibited higher antioxidant activity with 83.1% of inhibition (Fonseca *et al.*, 2019). Moreover, P80-Que-SeNCs not only showed low cytotoxicity in the presence of PC12 cells but also protected PC12 cells from damage by H_2O_2 (1000 µM) (Qi *et al.*, 2020). Fortification of snacks with resveratrol-nano-encapsulated in lotus-stem starch particles showed the highest inhibition value of lipid peroxidation (61.85%) compared to snacks with fortified non-encapsulated resveratrol (40.78%) (Ahmad and Gani, 2021).

Table 2. Health-promoting properties of some bioactive food compounds

Bioactive compounds	Health-promoting property	References
Silymarin	Hepatoprotective, antioxidant, antidiabetic anticancer, and cardioprotective activities	(El-Samaligy, Afifi and Mahmoud, 2006; Mukhtar *et al.*, 2020)
Luteolin	Antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic activities	(Boslett *et al.*, 2017; Bradwell *et al.*, 2018; Ramešová *et al.*, 2012)
Apigenin	Act as free-radical scavengers and antioxidants, exhibiting anti-mutagenic, anti-inflammatory, and antiviral effects	(Bradwell *et al.*, 2018; Salehi *et al.*, 2019b; Wang *et al.*, 2019b; Zhai *et al.*, 2013)
Tangeretin	Antioxidant, anti-inflammatory, antitumor, hepatoprotective, and neuroprotective effects	(Mizuno, Yoshikawa and Usuki, 2019; Ozkan *et al.*, 2020; Raza, Luqman and Meena, 2020)
Quercetin	Antioxidant, anti-inflammatory, antibacterial, antiviral, radical-scavenging, gastroprotective, and immune-modulatory activities	(Ciardi *et al.*, 2021; Dabeek and Marra, 2019; Pinheiro *et al.*, 2020; Qi *et al.*, 2020; Ramešová *et al.*, 2012; Sun *et al.*, 2016; Wang *et al.*, 2005)
Kaempferol	Antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, neuroprotective, antidiabetic, anxiolytic, anti-osteoporotic, estrogenic/antiestrogenic, analgesic, and antiallergic activities	(Saldanha *et al.*, 2019; Cid-Ortega and Monroy-Rivera, 2018; Dabeek and Marra, 2019; Wang *et al.*, 2005)
Myricetin	Antioxidant, anticancer, antidiabetic, and anti-inflammatory activities	(Franklin and Myrdal, 2015; Ozcan and Yaman, 2015; Taheri *et al.*, 2020)
Galangin	Antiviral, antimicrobial, antidiabetic, and anticancer properties, without side effects	(Sabry *et al.*, 2021; Zhu *et al.*, 2018)
Hesperidin	Antihyperlipidemic, cardioprotective, antihypertensive, and antidiabetic activities	(Majumdar and Srirangam, 2009; Zanwar *et al.*, 2014; Karim *et al.*, 2021)

(Continue Table 2)

Bioactive compounds	Health-promoting property	References
Naringenin	Antidiabetic, antiatherogenic, antidepressant, immunomodulatory, antitumor, anti-inflammatory, DNA protective, hypolipidaemic, antioxidant, peroxisome proliferator-activated receptors (PPARs) activator, and memory improving	(Zhang *et al.*, 2013; Salehi *et al.*, 2019a; Saldanha *et al.*, 2019; Zanwar *et al.*, 2014)
β-Carotene	Provitamin A, antioxidant, skin protection, antitumor, anti-inflammatory, antimicrobial, antidiabetic, and anticancer properties	(Lee *et al.*, 2020; Tan *et al.*, 2014; Stahl and Sies, 2005)
Pelargonidin	Antioxidant, anti-inflammatory, anti-obesity, anti-diabetic, cytoprotective, neuroprotective, and anti-cancer activities	(Shishir *et al.*, 2020; Rashwan *et al.*, 2022a; Rashwan *et al.*, 2021a)
Proanthocyanidins	Hepatoprotective, antioxidant, anti-obesity, anti-diabetic, anti-microbial, anticancer, and cardioprotective activities	(Rashwan *et al.*, 2022a; Beecher, 2004; Sorour *et al.*, 2017; Zineb *et al.*, 2022; Rashwan *et al.*, 2021b)
Curcumin	Antioxidant, antimicrobial, anti-obesity, antidiabetic, anticancer, anti-inflammatory, cardioprotective, anti-Alzheimer's, and anti-aging activities	(Ariamoghaddam *et al.*, 2018; Lazar *et al.*, 2013; Liu *et al.*, 2019; Pontes-Quero *et al.*, 2020; Shahgordi *et al.*, 2020; Sharma *et al.*, 2019; Rashwan *et al.*, 2022b)
Saponins	Molluscicidal, antimicrobial, antiparasitic anti-inflammatory, and haemolytic activities	(Cheok, Salman and Sulaiman, 2014)
Resveratrol	Antioxidant, antitumor, anti-inflammatory, cardioprotective, and neuroprotective activities	(Ahmad and Gani, 2021; Jayan *et al.*, 2019; Sanguansri *et al.*, 2013; Zupancic, Lavric and Kristl, 2015)
Tributyrin	Improve the gut microbiota composition, and treat inflammatory bowel disease	(Li *et al.*, 2021; Sanguansri *et al.*, 2013)
Eicosapentaenoic acid (EPA)	Numerous anti-atherosclerotic effects including antiplatelet aggregation, vasodilation, anti-inflammation, anti-Alzheimer's as well as lowering plasma TG	(Gu, Kavanagh and McClure, 2021)
Docosahexaenoic acid (DHA)	Anti-inflammatory, cardioprotective, anti-Alzheimer's, and anti-aging activities	(Calder, 2016; Stramarkou *et al.*, 2021)
Mangiferin	Antioxidant, antimicrobial, antidiabetic, antiallergic, anticancer, hypocholesterolemic, and immunomodulatory	(Khurana *et al.*, 2016; Varela-López *et al.*, 2015; Imran *et al.*, 2017)
Thymoquinone	Anti-convulsant, anti-microbial, anti-cancer, anti-histaminic, anti-diabetic, anti-inflammatory, and antioxidant activities	(Goyal *et al.*, 2017; Tabassum *et al.*, 2021)
Isorhamnetin	Antioxidant, antiviral, anticancer, antimicrobial, and anti-inflammatory effects as well as cardio-cerebrovascular and nerve protection	(Wang *et al.*, 2005; Gong *et al.*, 2020)
Capsaicin	Inhibits acid secretion, stimulates alkali and mucus secretion, and prevention and heals gastric ulcers, antioxidant and anti-inflammatory, anti-inflammatory, anti-obesity, anti-diabetic, cytoprotective, neuroprotective, antimicrobial, and anti-cancer activities	(Arunprasert *et al.*, 2022; Merritt *et al.*, 2022; Srinivasan, 2016)
N-Acetylcysteine	Reducing neomycin-induced ototoxicity *in vitro* and *in vivo*	(Wang *et al.*, 2022)
Coenzyme Q10	Plays an important role in mitochondrial ATP synthesis, antioxidant, antimicrobial, anti-obesity, antidiabetic, anticancer, anti-inflammatory, cardioprotective, anti-Alzheimer's, and anti-aging activities	(Cheng *et al.*, 2021; Mohsen *et al.*, 2021)

4.2. Antiobesity activity

Obesity is one of the serious diseases worldwide, which is the beginning of many health complications such as cardiovascular disorders, type 2 diabetes mellitus, and locomotor disease. Therefore, many researchers seek to develop and/or improve food supplements (drugs) from natural sources with fewer adverse effects, which can prevent and ameliorate obesity (**Table 2**) (Akolade, Oloyede and Onyenekwe, 2017; Ariamoghaddam *et al.*, 2018; Ahmad and Gani, 2021). For instance, nanoencapsulation of Cur in chitosan-based polyelectrolyte complexes improved the α-amylase inhibitory activity of Cur. In which, the oral administration of a sub-therapeutic dosage of Cur nano-encapsulated (50 mg/kg b.wt.) in chitosan-based complexes caused a significant reduction in hyperglycemia within 7 days of treatment (Akolade, Oloyede and Onyenekwe, 2017). The authors studied *in vivo* anti-obesity efficacy of Cur-loaded nanofibers transdermal patches in high-fat diet-induced obese rats. They found that Cur-loaded nanofibers reduced the total amount of adipose tissue (4 to 7%) estimated by a whole-body magnetic resonance imaging technique (Ariamoghaddam *et al.*, 2018). Snacks with fortified resveratrol-nano-encapsulated in horse-chestnut (HRP), water-chestnut (WRP), and lotus-stem starch particles (LRP) showed a higher inhibition percentage of pancreatic lipase than the snacks with non-encapsulated resveratrol. Inhibition of the pancreatic lipase by HRP, WRP, and LRP was 39.46, 44.46, and 24.86 % respectively, while the snacks with the fortification of resveratrol in free form showed significantly less inhibition percentage (18.93%) (Ahmad and Gani, 2021). Moreover, the snacks with nanocapsules of resveratrol showed a better inhibition percentage of cholesterol esterase than snacks with the fortification of free resveratrol. The inhibition percentage of cholesterol esterase by HRP. LRP and WRP were 64.76, 74.1, and 59.58%, respectively, while snacks with the fortification of free resveratrol showed comparatively very less inhibition (32.02 %) (Ahmad and Gani, 2021).

4.3. Antidiabetic activity

Diabetes is an ongoing disorder of the blood glucose level caused by an imbalance in the secretion or utilization of insulin. Diabetes and its effects can be reduced by controlling certain enzymes such as α-glucosidase and α-amylase. The encapsulated-bioactive compounds can assist to control the blood glucose level by controlling the diabetes triggers (i.e., delaying the carbohydrate metabolism process) (Perumal *et al.*, 2016; Sathiyaseelan *et al.*, 2020; Ahmad and Gani, 2021; Shishir *et al.*, 2020). Feeding diabetic rats on *Stevia rebaudiana* leaf extract-loaded in chitosan-nanoparticles (SRLE-CNP) showed a high reduction in their mean fasting blood glucose level compared to the diabetic control group. Besides, SRLE-CNP assisted to keep the serum levels of various enzymes such as serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatases, lipid peroxidation, and antioxidants (i.e., catalase, reduced glutathione, and superoxide dismutase) in the treated group were closer to normal levels than those in the diabetic control group (Perumal *et al.*, 2016). The time-dependent study revealed that Cur-activity for inactivating the α-amylase was enhanced via nano-encapsulating it in chitosan-based polyelectrolyte complexes. Whereas oral administration of 50 mg/kg b.wt. as a sub-therapeutic dosage of Cur nano-encapsulated in chitosan-based complexes caused a high reduction in hyperglycaemia within 7 days of therapy. This may be attributed to the ability of the chitosan-based polyelectrolyte complexes delivery system to improve the intestinal absorption of oral drugs to the relative pharmacological bioavailability conferred on such therapeutics by the carrier (Akolade, Oloyede and Onyenekwe, 2017). P3G-NL also showed the highest α-amylase inhibition activity was 59.78%. This could be attributed to the greater percentage of P3G release from NL during simulated small intestine fluid digestion (Shishir *et al.*, 2020). Moreover, synthesized fungal chitosan encapsulated *Gynura procumbens* mediated silver nanoparticles showed the inhibition of *α*-glucosidase and *α*-amylase at 3.6 and 7.5 μg/mL respectively (Sathiyaseelan *et al.*, 2020). *In vitro* study showed that snacks with fortified resveratrol capsules significantly reduced the α-glucosidase activity with inhibition values ranging from 23.23 to 63.23% compared to snacks with the fortification of resveratrol in free form (Ahmad and Gani, 2021).

4.4. Anti-amyloid activity (Anti-Alzheimer's disease)

Amyloid is an amorphous translucent substance consisting primarily of proteins that are deposited in extracellular of some animal's body tissues and organs under abnormal conditions (such as Alzheimer's disease (AD)) giving the disease known as amyloidosis. Encapsulated-bioactive compounds can decrease amyloid plaque formation (Khmara *et al.,* 2020; Pinheiro *et al.,* 2020; Qi *et al.,* 2020; Sharma *et al.,* 2019). Injection of Cur-conjugated nano-liposomes in the hippocampus and the neocortex of APPxPS1 mice was able to specifically stain the Aβ deposits *in vivo* (Lazar *et al.,* 2013). Another *in vivo* study showed that the injection of PLGA-Qu-NPs into APP/PS1 mice ameliorates cognition and memory impairments. Besides, *in vitro* (SH-SY5Y cells) study demonstrated that the effects of PLGA-Qu-NPs on inhibited and disassembled Aβ42 fibrils have low cytotoxicity. Cytotoxicity studies of the PLGA-Qu-NPs led to a concentration-related behavior on the SH-SY5Y human neuroblastoma cells, which also showed that PLGA-Qu-NPs inhibited the neurotoxicity of the Zn^{2+}-Aβ42 system and enhanced the viability of neuron cells (Sun *et al.,* 2016). Additionally, *in vitro* (cell culture) study showed that Cur encapsulated in mesoporous Fe-Phenanthroline nanocluster reduced amyloid-β plaque formation by 51.4% compared to untreated control (Sharma *et al.,* 2019). Permeability studies across hCMEC/D3 cell monolayers showed that quercetin-loaded lipid nanoparticles functionalized with transferrin (Qu-NLC-transferrin) have more ability to permeate the blood-brain barrier. Amyloid-beta studies also revelated that Qu-NLC-transferrin can inhibit fibril formation (Pinheiro *et al.,* 2020). Furthermore, thioflavin T (ThT) fluorescence assay, circular dichroism (CD) spectroscopy, and atomic force microscope (AFM) imaging results showed that P80-Que-SeNCs inhibited amyloid plaque formation, but P80-CA-Se NCs do not that (CA= citric acid). Additionally, intrinsic tyrosine fluorescence spectra confirmed that there were static quenching and strong interaction between the Aβ1–42 and P80-Que-SeNCs (Qi *et al.,* 2020). ThT assay and AFM microscopy analysis also showed the ability of chitosan-coated magnetite nanoparticles to interfere with α-lactalbumin amyloid fibrils (α-LAF), causes to the destruction of α-lactalbumin amyloid fibrils in a concentration-dependent manner (Khmara *et al.,* 2020). The study using transgenic mice (5XFAD) revealed that Se-PLGA is a great targeting delivery system to amyloid plaques, which provided the enhancement of therapeutic efficacy in AD lesions. Cur-loaded Se-PLGA nanospheres reduced the amyloid-β load in AD mice brains and greatly cured the memory deficiency of these mice (Huo *et al.,* 2019).

4.5. Anti-inflammatory and antinociceptive activities

Inflammation and nociceptive are related processes that share the same effectors and mediators. Pro-inflammatory molecules e.g., tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and prostaglandin E_2 (PGE_2) can act on peripheral terminals of neurons that are called nociceptors, causing their activation, and increasing pain sensitivity. Thus, anti-nociception can be defined as the action or process of blocking the detection of a painful or injurious stimulus by sensory neurons (Gehrcke *et al.,* 2018; Sharma *et al.,* 2019; Chen *et al.,* 2019). Generally, anti-inflammatory drugs are used for pain treatment in clinical practices, but these drugs showed several adverse effects. These effects are probably increased with the long-term administration of these drugs (Gehrcke *et al.,* 2018; Mattiazzi *et al.,* 2019). Therefore, the development of novel pharmacological alternatives to treat and control inflammation and pain has received special attention from the scientific community.

The authors evaluated anti-colitis activity (in the rat model) of Cur-asafoetida complex-encapsulated in turmeric-nanofiber. They found that the treatment with this complex significantly attenuated the disease activity index, colitis score, histopathological changes, and myeloperoxidase activity (Gopi *et al.,* 2017). Moreover, the Cur-asafoetida complex encapsulated in turmeric nanofiber showed significant protective effects against DSS induced colitis (Gopi *et al.,* 2017). *In vivo* (acute pain models) analysis, and time-response curve showed that both forms (free and nano-encapsulated) of indole-3-carbinol (I3C) inhibited the inflammatory phase of nociception induced by formalin and increased the latency response in the hot plate test. Interestingly, the I3C effect in both tests was prolonged after being

loaded in nanocapsules compared to free-I3C. Furthermore, in the dose-response curve, just the I3C-nano-encapsulated form showed an effect on the inflammatory phase of the formalin test (Gehrcke *et al.*, 2018). Additionally, the study in animals showed that both free and 3,3′-diindolylmethane (DIM)-loaded nanocapsules (NCs) decreased the mechanical hypernociception induced by complete Freund's adjuvant (CFA), mitigated nociceptive behavior of formalin-induced neurogenic and inflammatory pain and increased the paw (Mattiazzi *et al.*, 2019). However, only the DIM-nano-encapsulated promoted a rapid initiation and prolonged the bioactive antinociceptive action (up to 8 h) as well as reduced the effective dose. Cur-encapsulated in mesoporous Fe-Phenanthroline nanocluster declined the expression of TNF-α (93.4%), apolipoprotein E (90.4%), and IL-8 (90.7%) (Sharma *et al.*, 2019). The 25-hydroxyvitamin D_3-eluting nanofiber scaffolds significantly decreased the production of TNF-α and IL-6. However, it is accelerating the production of anti-IL-4, and -IL-10 within the scaffolds. Furthermore, 25-hydroxyvitamin D3-eluting nanofiber scaffolds increased the expression of human cathelicidin LL-37, while no LL-37 expression was observed in the control (Chen *et al.*, 2019). Betulinic acid-loaded polyvinyl alcohol/methylacrylate grafted lignin polymer decreased the lipopolysaccharides induced inflammation through the downregulation of NFκB and MAP/JNK signaling molecule expressions (Zhang *et al.*, 2021).

4.6. Anti-cardiovascular disease

Recently, cardiovascular diseases (CVD) are considered one of the important causes of death each year worldwide. Low-density lipoprotein cholesterol (LDL-C), also called "bad" cholesterol is one of the important causes that can be assisting to increase the CVD risk. LDL can deposit in the blood vessels, causing them to close or narrow these vessels. As a result, a heart attack, chest pain (angina), or stroke will occur (Wang *et al.*, 2019a; Earnest *et al.*, 2007). The study on Male Wistar rats revealed that Ingestion of pyridostigmine-encapsulated liposome induced a significant increase in the interval between the beginning of the Q-wave and the end of the T-wave (QT interval) (22.3% after 3.0 μg). The maximum effect of pyridostigmine in liposomal formulation preventing QT interval increase was observed 2 h after treatment (9.7% after 3.0 μg of NA) and was still present until 6 h when 1 mg/kg was previously administrated compared to the effect of free pyridostigmine that was only observed after 1 h for the dose of 0.3 mg/kg (6.8% after 3.0 μg of NA) and was no longer observed after 2 h of the treatment (Vidal *et al.*, 2010). Furthermore, a clinical study on 54 men and women (20 to 70 y of age) showed that ingestion of encapsulated-phytosterol ester (EPE) appeared a positive effect to modulate LDL-C. The statistical analysis revealed a significant within-group reduction in total cholesterol (TC) (−0.23 mmol/L) and LDL-C (−0.22 mmol) for the EPE group compared to the placebo group. In which, the percentages of change in TC and LDL-C for EPE treatment were −3.52% and −5.00%, respectively, while for placebo were 2.64% and 4.89 %, respectively, from baseline (Earnest *et al.*, 2007). *In vivo*, the consumption of nano-silica-quercetin-encapsulated PLGA nanocomposite (SiN-Qu-PLGA) fundamentally expanded the divider thickness to 51% of the control gathering. A striking divider thickness increment was watched for the SiN-Qu-PLGA aggregate where relative divider thickness was 80% of the control gathering. These outcomes show that SiN-Qu-PLGA improves the functional similitude to the local myocardium that permitting cell enlistment, attachment, expansion, and articulation of heart proteins (Wang *et al.*, 2019a). *In vivo* results showed that betulinic acid-loaded polyvinyl alcohol/methylacrylate grafted lignin polymer effectively reduced the hyperchlostremia, inflammation, and vasoconstriction, which induced over a high-fat diet. The results of histopathological analysis of cardiac tissues also assured the cardioprotective role of synthesized nanoformulation (Zhang *et al.*, 2021).

4.7. Hepatoprotective activity

Cumin essential oil extract (phenolic content)-loaded in nanoemulsions provided high hepatoprotective potential and reserved rats' body weight after seven days of a single transdermal application (Mostafa *et al.*, 2015). Nano-emulsions enhanced the stability, bioavailability, and cellular uptake of phenolic compounds as well as provided targeting delivery of phenolic compounds to the liver cells. Hence, the phenolic compounds may scavenge free radicals and regulate the activity

and/or expression of certain enzymatic systems implicated in relevant physiological processes e.g., the metabolism of xenobiotics in the liver, which reduced the levels of serum aspartate transaminase (AST) and alanine transaminase and alkaline phosphatase (ALP) contribution to hepatoprotective activity (Mostafa *et al.*, 2015). Poly(Ɛ-caprolactone)-loaded nanoparticles protected HepG2 cells from intrinsic compound toxicity at high concentrations. Depending on the incubation regimen, quercetin-biapigenin poly(Ɛ-caprolactone)-loaded nanoparticles or free compounds were more effective in protecting HepG2 cells against tBuOOH (tert-butyl hydroperoxide)-induced toxicity (Oliveira *et al.*, 2018). The tissue distribution studies showed that the encapsulated-galangin in liposomes was enriched in the liver and exhibited better hepatoprotective effects in CCl4-intoxicated mice compared with the non-encapsulated galangin. In which, the animals pretreated with encapsulated-galangin revealed lower ALT and AST levels than those pretreated with free galangin (Zhu *et al.*, 2018). This is probably due to the enhanced oral bioavailability and the passive liver targeting of the liposomes. Liposomes could penetrate liver sinusoids to interact with hepatocytes, hence, it increased the galangin hepatoprotective effects (Zhu *et al.*, 2018). In albino rats' study showed that consumption of encapsulated silymarin enhanced the target delivery and prevented the degradation of a bioactive component. Besides, the long-term induction of silymarin (300 mg/kg) significantly amplified the survival time of rats with paracetamol-induced hepatic injuries. This study also showed changes in liver fibrosis and a significant increase of hepatic enzyme biomarkers after consuming encapsulated-silymarin (Mukhtar *et al.*, 2020). The improvement of hepatoprotective activity of silymarin may be due to the enhancement of its solubility and bioavailability after encapsulation as well as the presence of a high level of antioxidants, such as flavonoids, vitamin A, vitamin C, and α- and β-carotenes (Mukhtar *et al.*, 2020). The *in-vivo* study revealed that Co-Q10-cubosomes improved hepatoprotective effect by reducing liver enzymes, nitric oxide, and malondialdehyde as well as elevating phosphoinositide 3-kinase, catalase, and glutathione peroxidase, compared to the normal drug (Mohsen *et al.*, 2021).

4.8. Antimicrobial and anti-biofilm activities

A biofilm also known as microbes' cities (microbes-storehouse), comprises any syntrophic consortium of microorganisms in which cells stick to each other on the surface of materials (foods). These adherent cells become embedded within a slimy extracellular matrix that is composed of extracellular polymeric substances. These polymeric substances such as polysaccharides, proteins, lipids, and DNA, which are caused the destruction and spoilage of food or infected materials (Heidari *et al.*, 2020; Kumari *et al.*, 2020). Therefore, encapsulation systems have been used to increase the antimicrobial activity of drugs (bioactive compounds). Tannic acid-loaded niosome reduced biofilm formation capacity in *Escherichia coli* (*E.coli*), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (*S. aureus*) and down-regulated the biofilm gene expression as compared to free tannic acid (Heidari *et al.*, 2020). Moreover, Cur-PLGN displayed strong antibacterial efficacy against *E. coli* and *S. aureus*, compared to non-encapsulated-Cur. Cur-PLGN also disrupted the biofilm formed by these bacteria (Kumari *et al.*, 2020). Cinnamaldehyde-encapsulated in liposome (CEL) significantly inhibited the growth of *Aeromonas hydrophila* (*A. hydrophila*), *Vibrio vulnificus* (*V. vulnificus*), and *Streptococcus agalactiae* (*S. agalactiae*), even inhibited the antibiotic-resistant such as *Vibrio parahaemolyticus* and *Vibrio alginolyticus*. Bacteria challenge test results showed that CEL significantly improved the survival rate and reduced bacterial growth in zebrafish (*Danio rerio*) infected with *A. hydrophila*, *V. vulnificus*, and *S. agalactiae* (Faikoh, Hong and Hu, 2014). The starch electrospun nanofibers loaded with 30% carvacrol reduced bacteria growth by approximately 89.0% for *Listeria monocytogenes* (*L. monocytogenes*), 68.0% for *Salmonella Typhimurium*, 62.0% for *E-coli*, and 49.0% for *S. aureus*. These electrospun nonwovens sustained antimicrobial activity for at least 30 days against *S. aureus* (Fonseca *et al.*, 2019). The embedding of oregano essential oil into chitosan/poly(ε-caprolactone) nanofiber mats exhibited distinctive antibacterial activity towards Gram-positive (*S. aureus*, *L. monocytogenes*) and Gram-negative (*Salmonella enteritidis*, *E-coli*) bacteria (Hasanpour Ardekani-Zadeh and Hosseini, 2019). Synthesized fungal chitosan

encapsulated *Gynura procumbens* mediated silver nanoparticles showed minimal inhibitory concentration for *Bacillus cereus*, *S. aureus*, *L. monocytogenes*, *E. coli*, and *Salmonella enterica* approximately 8.12, 4.08, 4.95, 8.25, and 4.12 µg/mL, respectively (Sathiyaseelan *et al.*, 2020).

4.9. Immune-modulatory activity

The human immunodeficiency virus (HIV) has infected approximately thirty-eight million people worldwide in recent years. Consequently, an increase in the number of people with HIV causes a gap in antiretroviral therapy coverage among these people (UNAIDS, 2020). Therefore, many scientists are trying to develop treatments that assist to treat HIV, immune-modulatory, or reducing symptoms of it. They use nanotechnology to encapsulate bioactive compounds for this purpose (Clayton *et al.*, 2009; Zhao *et al.*, 2017; Faikoh, Hong and Hu, 2014; Shahgordi *et al.*, 2020). The antiviral study showed that a protease inhibitor PI1 concentration of 0.1 µM in F105-L-PI1 formulation (F105 Fab'-conjugated liposomes (F105-L-PI1)) inhibited approximately 80% of viral replication for the entire duration of the experiment compared to only 20% and 10% inhibition by L-PI1 or as free PI, respectively. These results confirmed that the PI1 delivered via the immuno-liposomes showed higher and longer antiviral activity than comparable concentrations of non-encapsulated drug or drug-encapsulated liposomes without targeting. Hence, a combination of targeting moiety with drug-loaded liposomes, efficient and specific uptake by non-phagocytic HIV-infected cells was facilitated, resulting in drug delivery to infected cells (Clayton *et al.*, 2009). Furthermore, encapsulated bioactive compounds can reduce peripheral neuropathy which became the most common neurological complication in patients with human immunodeficiency virus (HIV) (Zhao *et al.*, 2017). *In vivo* experiments (male Sprague-Dawley rats) explored the effects of nanoparticle-encapsulated Cur (nano-Cur) on HIV-gp120-induced neuropathic pain mediated by the $P2X_3$ receptor in dorsal root ganglia (DRG) neurons. The results confirmed that therapy of animals via nano-Cur caused the reduction of mechanical hyperalgesia and thermal hyperalgesia and upregulated the expression levels of $P2X_3$ mRNA and protein in rats treated with glycoprotein 120 (gp120). Besides, the nano-Cur therapy decreased the ERK1/2 phosphorylation levels in the gp120-treated rats (DRG). Moreover, P2X3 agonist α, β-methylene ATP (α, β-meATP)-induced currents in DRG neurons cultured with gp120 significantly reduced after co-treatment with nano-Cur (Zhao *et al.*, 2017). A gene expression study using a real-time PCR showed that LEC immersion-treated *Danio rerio* had increased endogenous IL-1*β*, IL-6, IL-15, IL-21, TNF-*α*, and interferon-*γ* (INF-*γ*) expression *in vivo*. After the *Danio rerio* were infected with *V. vulnificus* or *S. agalactiae*, the LEC immersion treatment suppressed the expression of the inflammatory cytokines IL-1*β*, IL-6, IL-15, NF-κb, and TNF-*α* and induced IL-10 and C3b expression. Hence, these results indicate that LEC has immune-stimulating effects to protect the host's defenses against pathogen infection in bacteria-infected *Danio rerio*. Therefore, LEC could be used as an immunostimulant to protect bacteria-infected fish in aquaculture (Faikoh, Hong and Hu, 2014). The researchers studied the effect of encapsulating Cur (Cur) and ovalbumin (Ova) in polylactic co-glycolic acid nanoparticles (PLGA-NPs) on sublingual immunotherapy (SLIT) efficiency in the mouse model of rhinitis allergic. They found that SLIT treatment with Cur+Ova-PLGA-NPs reduced the total IgE. Besides, PLGA-Ova (equal to 5µg Ova) + Cur (10µg) and PLGA-Cur (equal to 5µg Cur) + Ova (5µg)), showed the highest level of IFN-γ:IL-4 compared to control (Shahgordi *et al.*, 2020). Nasal lavage fluid analysis also showed that the levels of total and eosinophil cell count were significantly decreased in the treated nano-formulation groups. In addition, the histopathological results of nasal lavage fluid in treated mice were normal with no cellular infiltration and no inflammation (Shahgordi *et al.*, 2020).

4.10. Anti-cancer activity

Treatment of S180 tumor in mice using Tf-PEG-NP loaded with PEGylated drug conjugates showed the most powerful inhibition tumor activity rate up to 93% (1.85-fold, 1.23-fold that of PEG-HCPT and HCPT-loaded counterpart, respectively) (Hong *et al.*, 2010). *In vitro*, the cytotoxicity (a cell toxicity assay) of apigenin-loaded polymeric micelles showed higher activity against HepG2 and MCF-7 cancer cells than the

free drug (Zhai *et al.*, 2013). In a controlled and sustainable manner, treatment of DLD-1 cancer cells by saponin-encapsulated montmorillonite-human serum albumin nanocomposites showed a high devastating effect (Akbal *et al.*, 2018). Cur-loaded nanoemulsion showed a significant cytotoxic effect against cancer cells, in line with a notably lower cytotoxic effect towards normal lung fibroblast, where encapsulation raised its safety profile compared to free-Cur (Nikolic *et al.*, 2020). Cur-PLGN also showed high HepG2 cells cytotoxicity, while found to be cytocompatible toward HEK293 cells (Kumari *et al.*, 2020). Encapsulated *Trachyspermum copticum* essential oil into niosome showed higher cell toxicity against hepatocellular carcinoma cell line (HepG2) than free Trachyspermum copticum essential oil (Trinh *et al.*, 2019). The incorporation of galangin in niosomes improved its anti-tumor activity against liver cancer. Histopathological and immunohistochemical examination showed that galangin incorporated into niosomes exhibit a marked decline in minichromosome maintenance 3 immunostaining hepatocytes and neoplastic hepatic lesions with a small number of hepatic adenomas (Sabry *et al.*, 2021). Encapsulation of tocotrienols (TC) and caffeic acid (CA) in water-in-oil-in-water (W/O/W) multiple nanoemulsion with cisplatin (CP) synergistically enhanced the apoptosis in the late apoptotic phase in A549 and HEP G2 by 23.1% and 24.9%, respectively. Moreover, the generation of ROS was improved using TC: CA: CP by 16.9% and 30.2% for A549 and HEP G2, respectively. TC and CA encapsulated in W/O/W with CP also enhanced the cell arrest in the G0/G1 phase for both A549 and HEP G2. Besides, it led to cell death in A549 and HEP G2. For HEK 293, using TC, CA, and CP showed >95% cell viability while only ~33% cell viability was observed when only CP was used (Raviadaran *et al.*, 2021).

5. Conclusion and future directions

Plant, microbes, and animals are considered the main sources of bioactive components including polyphenols, flavonoids, ω-3 FAs, and so on. BFCs have many biological functions such as antioxidant, antidiabetic, antiobesity, anti-cardiovascular, anticancer, anti-inflammatory, antimicrobial, immune-modulatory, cholesterol reduction characteristics, and others. However, incorporation of BFCs in food or pharmaceutical formulations is limited because of their high liability against temperature, pH, shear, pressures, and light, as well as poor hydro-solubility in some of these compounds, and low stability under human gastrointestinal conditions, thereby lowing their bioavailability (BA) and losing functional activity. Therefore, encapsulation of BFCs using micro/nanostructure systems can overcome these challenges. These encapsulation systems include nano-silver, nano-gold, nano-emulsions, liposomes, cubosomes, biopolymer-based nanoparticles, nano-gels, and so on. Among them, biopolymer-based nanoparticles and nano-gels are the better choices to encapsulate the BFCs due to their advantages. Besides, encapsulation systems improved the bio-efficacy of BFCs including antioxidant, antidiabetic, antiobesity, anti-cardiovascular, anticancer, anti-inflammatory, antimicrobial, and immune-modulatory. Encapsulated curcumin and -quercetin showed the highest bio-efficacy compared to other encapsulated-BFCs. Finally, further studies are required to overcome the limitations related to micro-/nano-encapsulation techniques, improve the existing methods, and develop a new encapsulation system. Besides, further biological studies including clinical-based studies are recommended to explore the BA of BFCs-encapsulated micro-/nanoparticles.

Credit authorship contribution statement

Ahmed K. Rashwan: Conceptualization, Methodology, Writing- original draft, Writing - review & editing. **Hala A. Younes:** Methodology, Writing- original draft, Writing - review & editing. **Naymul Karim:** Methodology, Writing-original draft, Writing-review & editing. **Eman E. Taha:** Writing- original draft, Writing - editing. **M. R. Mozafari:** Writing- original draft, Writing - editing. **Hesham Z. Tawfeuk:** Writing- original draft, Writing - editing. **Wei Chen:** Supervision, Resources, Conceptualization, Methodology, Writing-original draft, Writing-review & editing.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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