SEVEN
publicações acadêmicas

Nanoencapsulation of flavonoid bioactives using the nanoprecipitation technique – Review

Crossref doi
https://doi.org/10.56238/Connexpemultidisdevolpfut-180

Marina da Silva Sacramento
Federal University of Rio de Janeiro, Institute of Macromolecules Professor Eloisa Mano, Av. Horácio Macedo 2030, Bl J, Centro de Tecnologia, Ilha do Fundão, Rio de Janeiro, RJ, Brazil, Cep 21941-598

Maria Inês Bruno Tavares
Federal University of Rio de Janeiro, Institute of Macromolecules Professor Eloisa Mano, Av. Horácio Macedo 2030, Bl J, Centro de Tecnologia, Ilha do Fundão, Rio de Janeiro, RJ, Brazil, Cep 21941-598

ABSTRACT
Various food processing industries have been focusing on creating new foods from functional foods due to the growing demand for healthier habits. The class of flavonoids has significant therapeutic potential, with antioxidant and anti-inflammatory attributes attributed to the bioactives present in functional foods. Nanoencapsulation carried out through the nanoprecipitation technique is an effective method to encapsulate these bioactives in polymeric matrices, allowing the generation of a material with a longer shelf life, extracted from these types of foods. This enables the production of nutraceuticals, with a focus on generating dietary supplementation/improvement for human health. Thus, the objective of this seminar was to present studies on bioactives with antioxidant properties, derived from the flavonoid group, nanoencapsulated through the nanoprecipitation technique. This technique demonstrated efficacy in the generation, bioavailability, and shelf life enhancement of nutraceuticals.

Keywords: Nanoprecipitation, Nutraceutical, Bioactives, Polymeric Matrices.

1 INTRODUCTION

Increasingly, the population has been paying attention to healthier habits, such as a balanced diet that results in a beneficial functioning of the body in order to prevent diseases. The implementation of a healthy diet should contain foods considered functional, which have bioactive compounds, which bring health benefits.

Research on food has increased due to the identification of its main bioactives, which have important properties for the body. These foods are called functional foods that are part of a usual diet in order to exert benefits for the improvement, control and prevention of chronic non-communicable diseases (NCDs), ranging from changes in the cardiovascular systems, type 2 diabetes, permeating by various types of cancer. The properties of bioactives have led to the generation of nutraceutical systems, which are food supplements, which when consumed daily can exert beneficial effects on human health.

Research conducted by the Brazilian Association of the Food Industry for Special Purposes and Congeners (Abiad) (2020) reports a deficit in the intake of functional foods containing bioactives

with recognized properties such as: antioxidant, antiinflammatory, antimicrobial, antifungal, antiglycemic, anticancer actions, among others. This deficit has contributed to an increase and worsening of vascular diseases that are interconnected with various pathologies caused by the increase in blood glucose, which consequently causes the obstruction of cardiovascular arteries, externalizing new diseases in the body.

However, according to an article publication platform, the number of scientific documents on bioactive compounds in the flavonoid class has increased significantly in recent years, with a growth trend of 45.28% from 2016 to 2021 (Scopus Database, 2022).

ABIAD (2020) showed in a study carried out in seven capitals of Brazil, that in at least 59% of Brazilian households, there is a person using nutraceuticals, a habit being mostly female. Justifying the use of the food supplement due to the fact that 87% of the interviewees ate their meals away from home, having the need for food supplementation. ABIAD (2020) also found that most consumers increased their consumption during the Covid-19 pandemic and continued with the new habits, as they identified an increase in willingness and a greater sense of security regarding immunity.

According to Reza and Kristen (2014), it is essential to implement foods containing bioactives, which can be in the form of nutraceuticals or as a food supplement, so that this bioactive acts in the formation of free radicals, protecting the human body from the development of inflammation.

Nanoencapsulation acts as a technique capable of contributing to the protection of the bioactive, since this substance can exhibit a high instability, allowing degradation due to variation in temperature, humidity and pH. In other words, this is a technique that aims to protect the active substances by means of a membrane (NESTERENKO *et al., 2013), which can be formed by biodegradable polymers, polysaccharides, proteins, gums, and lipids* (PEREIRA et al., 2018), *evidencing many advantages ranging from flavor alteration to the controlled release of the substance into the body* (DUBEY; SHAMI; BHASKER RAO, K.U, 2009; NESTERENKO *et al*., 2013).

It is important to emphasize that for the success of the nanoencapsulation technique it is necessary to know the substances that are present in the food of interest, how they will be extracted and what will be the material used for nanoencapsulation. This knowledge can be obtained and confirmed by characterization techniques such as ultraviolet-visible spectroscopy (UV-VIS), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR).

The food industry has been increasingly exploring encapsulation and nanoencapsulation technology, as it promotes the generation of a differentiated commercial product, with innovations, being economically viable for the benefits that will be incorporated into health. As previously explained, the objective of this seminar is to present the bibliographic survey of studies of bioactives

extracted from functional foods with antioxidant properties of the group of nanoencapsulated flavonoids through the nanoprecipitation technique.

2 FUNCTIONAL FOODS

Decree-Law 986/1969 – Says that "any substance or mixture of substances, in the solid, liquid, pasty or any other suitable form, intended to provide the human organism with the elements normal to its formation, maintenance and development are considered as food". The definition of Functional Foods was presented in Japan, in the 1980s, with the termology "*Foods for Specified Health Use*" (FOSHU), as being foods similar in appearance to conventional foods, but which demonstrated health benefits (HASLER, 1998). However, in the literature there are several definitions for functional foods, such as foods or food ingredients that can provide some health benefit, in addition to the traditional nutrients already contained (Zakir and Freita, 2015).

In Brazil, the Technical-Scientific Advisory Committee on Functional Foods and Novel Foods (CTCAF) of the National Health Surveillance Agency (ANVISA) analyzes and approves new foods and ingredients, through their functional properties and health properties, establishing guidelines for their use. Thus, calling them "foods with claims of functional and/or health properties" (ANVISA, 2021).

In this way, it is understood that everything that can be ingested in liquid, pasty or solid form, which has the function of nutrition is considered a food. In addition, food containing bioactives, which are organic molecules of low molar mass, causing various effects on living organisms associated with behavior, physiology, or metabolism, becomes a functional food (ANVISA, 2021).

2.1 BIOACTIVES

According to Silva (2015), bioactives are natural compounds of plant or animal origin with beneficial properties for health, in addition to essential nutrition. De Vos et al. (2010) add that bioactive compounds beneficial to health that are used as functional foods include vitamins, minerals, peptides, fatty acids, probiotics, prebiotics, proteins, phytosterols, phytochemicals, and soluble and insoluble fibers.

The Brazilian legislation evaluates some registered bioactive substances with functional properties, such as: phenolic acids, fatty acids (monounsaturated ω-3 and ω-6), beta-glucan (soluble fiber), carotenoids (lycopene, lutein and zeaxanthin), resistant dextrin, phytosterols, fructooligosaccharides (FOS), partially hydrolyzed guar gum, inulin, dietary fibers, flavonoids, phospholipids, organosulfur acids, polyphenols, lactulose, polydextrose, polyols (mannitol, sorbitol, xylitol), probiotics, soy protein and Psillium (Plantago ovatae). These must be obtained from plants, animals, minerals, microorganisms, fungi, algae or synthetically (ANVISA, 2021).

Among the main bioactives, the flavonoid group and its special classes such as: flavonols, flavone, flavones, flavanones, isoflavonoids and anthocyanins stand out.

2.2 GRUPO DOS FLAVONOIDES

The Hungarian scientist Dr. Albert Szent-Gyorgy, in 1930, winner of the Nobel Prize in Medicine and Physiology, discovered that a class of compounds had the ability to fortify the walls of capillaries, favoring the function of Vitamin C, which has as its main function the maintenance of protein levels (collagen) in the body for the formation of bone tissues. skin, cartilage, etc. Initially, this discovery was classified as Vitamin P, and later identified that isolating a new chemical substance from oranges would improve absorption and protection against oxidation, finding that it was a flavonoid (SIES, 2020). Flavonoids are a group of substances composed of several classes such as: Flavonols, flavans, flavones, flavanones, isoflavonoids, and anthocyanins, which exert a primary role in protecting against oxidants, acting against free radicals, which means that this bioactive performs an effective protective action against oxidative processes that occur in the body spontaneously (MOHAMED *et al*., 2018). They also act as phenolic compounds that interact synergistically with other compounds, notably carotenoids and chlorophylls (well-known colored molecules) responsible for the unique color and aroma of fruits and vegetables (Karak, 2019).

This bioactive can be found in foods derived from: fruits, vegetables, grains, legumes, soybeans and teas (ROMAN *et al*., 2019). It is common to find more than one class of flavonoids in a given food, however some classes are found in larger proportions. This bioactive has its concentration established with the association of the color of a particular food (MOHAMED *et al*., 2018). In this way, foods with more intense color have more flavonoids of a certain class. The color of this bioactive can vary from violet to colorless, with the most intense coloring, with the potential to be used as a food coloring (ANJO *et al*, 2021), as shown in Table 1. These foods have shown, in addition to biological activities in vivo, *such as modulation of enzymatic activity and inhibition of oxidative proliferation, the confirmation of antioxidant activity* in vitro *and* in vivo *(*Romani et al., *2020*; Ahmed *et al*., 2016).

In addition to the antioxidant action and many other particularities, this bioactive can have antimicrobial properties. In a study carried out by Cowan (1999), the medicinal properties of propolis were cited, being for the treatment of wounds and ulcers by Hippocrates[1] in Ancient Greece. Cushnie & Lamb (2005) add that these antimicrobial properties refer to the action of its flavonoids: *galangin* and *pinocembrin*. The Chinese herb *Scutellaria baicalensis* is another example attributed to the flavone

[1] Hippocrates was considered the "father of Western medicine". He was an Athenian icon of the rejection of superstitious and mythical explanations for health problems and how to cure diseases.

baicalein, where it has been referred to its topical use as a systemic to treat periodontal abscesses and oral infections.

In order to acquire different health benefits, it is necessary to know the types of bioactives of their certain classes, in order to consider the amount of concentration to be used in the procedure to result in a commercial product. To put this into context, research on the practice of dietary supplementation intake has shown a continuous growth among Brazilians, moving billions of dollars in Brazil in 2020 (Euromonitor international, 2020).

Table 1: Classification of flavonoid groups and dietary identification.

Class	Colouring	Types	Foods	Source
Anthocyanins	Red and violet	Pelargonidina, Cianidina, dolphins, peonidina, petunidina e malvidin	*Cranberry*, strawberry, blueberry, raspberry, purple grape, eggplant, red cabbage, hibiscus, etc.	Orlikova *et al*., (2011); Kaushal, M.; Singh, M.; Rodriguez-Amaya, (2019); Sangwan, R. S., (2022)
Flavanas	Colorless	Catequinas, proanthocyanidins, catechin, epicatechin, epigallocatechin	Black tea, white and yellow teas, grapes and red wine.	He *et al*., (2021); L *'et al*., (2022); Caracas, (2019); Kumar; Pandey, (2013)
Flavonols	Yellowish	Quercetin, rutin, myricetin (MRC), kaempferol and fisetin.	Fruits such as citrus, plums, peaches, grapes, apples, other fruits and vegetables, except algae and fungi.	Frutos *et al*., (2019); Kaushal, N.; Singh, M.; Sangwan, R. S. (2022); Karak, (2019); Kumar; Pandey, (2013).
Flavanonas	Yellowish	Neohesperiphane, Hesperpereth, Rigerant and Narigenina.	Fruits such as citrus, berries, plums, peaches, grapes, and apples.	Frutos *et al*., (2019).
Flavononas	Yellowish	Destroyed, Destroyed	Citrus fruits.	He *et al*., (2021).
Flavonas	Yellowish	Anger, Swallowed by the Dragon, rutin, chrysin, apigenin and luteolin.	Mandarins, broccoli, apple, mint, celery, propolis, herbs, parsley, grapes, spices, cereals, other fruits.	Karak, (2019); Kumar; Pandey, (2013).
Isoflavonóides	It has no coloring	If you've been a member of your family, you've never been a member of the United Nations.	Legumes, soja	Alshehr i *et al*., (2021).

3 NACETICALS

The term nutraceutical has been used in recent years, and is internationally recognized as isolated or purified food products (LIRA *et al*., 2009; ESPÍN *et al., 2007), which in its encapsulated form contains the bioactive compounds extracted from functional foods (Liu* et al., *2019*), nutraceuticals demonstrate a beneficial physiological evolution to human health, such as prevention, maintenance, and treatment of chronic non-communicable diseases (Aronson, 2017; Liu *et al*., 2019).

In many moments, there is a misunderstanding of the concepts of nutraceuticals and pharmaceuticals, however, they are distinct. As mentioned earlier, nutraceuticals originate from the bioactive substances that are extracted from functional foods, and can then be encapsulated, resulting in a marketable product, which is considered a food supplement. The drug, according to ANVISA, "is an active chemical substance, drug or raw material that has pharmacological properties for medicinal purposes, used for diagnosis, relief or treatment, used to modify or exploit physiological systems or pathological states, for the benefit of the person in whom it is administered" (ANVISA, 2021).

Institutions such as the Brazilian Association of the Food Industry for Special Purposes and Congeners (Abiad), the Brazilian Association of Nutritional Products Companies (Abenutri) and the Brazilian Association of Nutritional Supplements and Food for Special Purposes (Brasnutri) also contribute to the monitoring of the production of economic aspects, import and export, daily consumption habits and eating behaviors. ANVISA is responsible for resolutions, technical notes, guides, ordinances, other legislation and several Brazilian guidelines pertaining to food supplementation.

Data from *Euromonitor International* (2020) report that Brazil had a large trade in nutraceuticals with a turnover of US$ 35 billion per year. ABIAD (2022) found a cumulative turnover of US$ 259.9 million in food supplements and vitamin supplements in 2021, correlating an increase of 10.8% over the previous year.

4 NANOENCAPSULATION AND NANOPRECIPITATION

About 60 years ago, encapsulation was developed in order to coat solid, liquid or gaseous substances. This technique consists of creating an outer coating/membrane on top of another material, with the justification of preserving the main substance of degradation, assisting in the controlled release in the desired area, and altering undesirable odors and flavors (SAIFULLAH *et al*., 2019).

According to Barreto (2015), the encapsulated material is called the filling or core and the material that forms the capsule is called the encapsulant, cover or wall. When it comes to size, capsules can be classified into macroparticles, microparticles, and nanoparticles. Such particles, when they are above 5,000 µm, are called macroparticles, when they have a diameter between 0.2 and 5,000 µm, they are considered microparticles, and when they have a diameter of less than 0.2 µm, they are classified as nanometric (SILVA *et al*., 2014; PEREIRA *et al*., 2018).

The most commonly used nutraceutical forms of this technique are nanospheres and nanocapsules, for the preparation of nanoparticles (RIVAS *et al*. 2017). Nanocapsules are vesicles with circular structures that form a polymer wall, in which the nutraceutical remains confined. Nanospheres are particles in which bioactives are dissolved or dispersed within the polymer matrix. (NAZLI; SAFIYE; EREM, 2018).

The pharmaceutical industry began to commercialize the encapsulated drug acetylsalicylic acid, aspirin, in tablet form, at the end of the nineteenth century. Research points to the possibility of much smaller particles, which consequently decreases the economic value of production, along with the paramount importance that the drug or food supplement reaches the desired location in the body. That is, so that it has a controlled release, allowing better the effectiveness of the process in the body, since the variation in the body's pH, enzyme production, body temperature and other variables are highly influential for the success of human supplementation (BAYER, 2022).

Nesterenko et al. (2013) state that the release of the filling can be triggered by shearing, solubilization, heating, pH alteration or enzymatic action. Simões et al. (2017) pointed out that the selection of the method for encapsulation depends on the properties of the core and wall materials, expected release rate, processing steps, particle size, and final application of the encapsulated particles.

The choice of the material to be used as a filling should consider factors such as: physical and chemical properties of the active agent such as porosity and solubility; of the covering material itself such as viscosity, stability, mechanical properties, glass transition, ability to form films, etc.; compatibility between the active agent and the wall material; and economic factors (REBELLO, 2009).

In view of this, there are numerous advantages of nanoencapsulation, such as: protection of sensitive substances to the environment, increased stability (protection against oxidation and reaction with other substances), controlled release of active substances, masking of unpleasant taste and odor, conversion of liquids into solids, less quantity used in the nanoencapsulated substance and low economic value (DUBEY; SHAMI; BHASKER RAO, 2009; NESTERENKO *et al*., 2013).

As previously mentioned, nanoencapsulation is necessary since bioactives have low stability, since it is possible to degrade the main active compounds by the action of heat and light, until their final destination and during storage (RODRÍGUEZ *et al*., 2016). Due to these delicate characteristics SHISHIR *et al.*, (2018), justify that this is a practice widely used in the food industry due to the protection provided to bioactives in terms of thermal degradation, microbiological stability, in addition to providing an adequate concentration of this to the organism.

SAIFULLAH et al. (2019) indicate three categories of techniques for nanoencapsulation at the nanometric scale, which are chemical, physical and physicochemical. He mentions as physical methods: nanoprecipitation, spray dryer, spray-cooling, thermal bath spraying, fluidized bed, centrifuge with multiple orifices, and as chemical methods: molecular inclusion and interfacial polymerization. Physicochemical methods include the following processes: coacervation or phase separation, emulsification followed by solvent evaporation, spraying in crosslink-forming agent, and liposomal involvement (SAIFULLAH *et al*., 2019; Neves *et al*., 2019; Otálora *et al*., 2019; Zanoni *et al*., 2020; Brito de Souza *et al*., 2020; Elik *et al*., 2021; Mutukuri *et al*., 2021).

According to GANGURDE et al. (2016), the type of wall material is of paramount importance to stabilize and be efficient in the protection capacity of the powdered product. The ideal wall material should have numerous properties, such as: 1) Being a good film former at the interface; 2) Have low viscosity at high concentrations of solids; 3) Display low hygroscopicity; 4) Release the nanoencapsulated material when desirable at the chosen location; 5) Have low cost; 6) Present high availability; 7) Offer good protection to nanoencapsulated substance. In order to promote a wall material considered ideal with reference to the properties listed above, biodegradable and biocompatible polymers are usually chosen in order not to generate any type of reaction to the immune system, such as poly-ε-caprolactone (PCL); Poly(D,L-lactic acid-glycolic acid)-block-poly(ethylene glycol)Carboxylic acid (PLGA-PEG-COOH); Polylactide (PLA); Poly(lactic acid-glycolic acid) (PLGA); among others.

A great incentive to research in this area of activity is the vast difficulty encountered in the nanoencapsulation of highly lipophilic substances, which have affinities and are soluble to fats, vegetable oils and lipids in general. The setback in nanoencapsulating these substances together with the time of processing, storage and commercial use causes it to suffer the action of oxidation (developing rancidity and altering sensory characteristics) and having considerable losses in its chemical composition (GANGURDE *et al*., 2016).

Nanoprecipitation is a method for performing nanoencapsulation, which is based on the precipitation of an organic phase in the aqueous phase, forming a colloidal suspension, by agitation. Fessi *et al*. (1989) *apud* Tavares (2016) report that In this method, it is essential to prepare two phases: organic phase and aqueous phase. The organic phase is composed of the polymer, an active substance, and a semi-polar organic solvent (miscible in water, such as acetone). In the aqueous phase, the surfactant is placed and, in sequence, one phase is added to the other under moderate magnetic agitation. MILADI *et al*., (2016) explains that in the Aqueous phase A surfactant is used to prevent agglomeration of nanoparticles.

FESSI *et al., (1989*) apud *LEPELTIER* et al., (2014) show that in this method the diffusion of the organic phase over the aqueous phase occurs, the latter being kept under constant agitation. The mixture of solutions becomes non-solvent for the hydrophobic molecules. With this, a colloidal suspension of nanoparticles is obtained. XIE et al. (2013) point out that there is a diffusion of the solvent in the decrease of the interfacial tension between the two phases, which results in an increase in the surface area and leads to the formation of small micelles. Rivas et al. (2017) stated that then there is the evaporation of the organic solvent at room temperature or with a rotaevaporator, which allows the production ofnanosuspension, which is considered a colloidal dispersion at the nanometric scale stabilized by a polymer and/or surfactant, presenting a milky appearance. In the next step, the

removal of the aqueous phase is used with the use ofutracentrifugation and , after freezing the sample and the freeze-drying process.

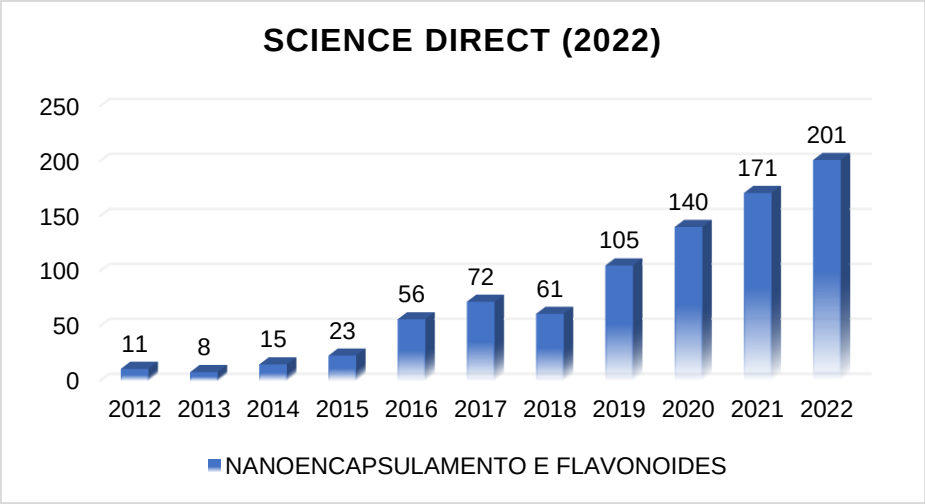
This method has numerous advantages in its use, such as:

A. Simplicity, speed and ease of realization;
B. It allows reproducibility between batches of nanoparticles;
C. Obtaining monodisperse formulations;
D. It is a cost-effective method;
E. The formation of the nanoparticles occurs instantaneously;
F. It has a high capacity to carry the drug or food supplement;
G. It allows the achievement of stable suspensions of both nanocapsules and nanospheres;
H. It allows the encapsulation of poorly soluble or even water-insoluble drugs/food supplements, increasing their bioavailability in the body;
I. Allows for easy control of particle size and polydispersion;
J. Moderate agitation;
K. It is capable of generating nanoparticles with a narrow size distribution, ranging from 50 nm to 300 nm;
L. Improvement in the thermal and chemical stability of bioactives.

5 STUDIES OF NANOPRECIPITATION USING FLAVONOIDS

A search for research on the keywords nanoencapsulation and flavonoids in the last 10 years on the *Science Direct* platform resulted in a significant increase in studies on this topic. The numbers range from 11 for the year 2012 to 201 for the year 2022, as shown in Figure 1. This growing number of published articles indicates the high interest in the commercial market in developing nutraceuticals with the preservation of the efficiency of bioactives from functional foods and extending their time for consumption.

Figure 1: Graph of scientific studies on nanoencapsulation and flavonoids.



Abu-Taweel et al. (2020); Feltrin et al. (2022); Minetti et al. (2022) researched the encapsulation of curcumin by the nanoprecipitation method. Dhas and Mehta (2021) produced nanoparticles formed by chitosan and PLGA containing curcumin (Cur), using the nanoprecipitation method in order to encapsulate hydrophobic drugs. The entire study was carried out in a comparative manner using the following polymeric systems: PLGA, Cur-laden PLGA NPs (Cur-PLGA NPs), chitosan-coated PLGA (CH@PLGA C/S NPs) and chitosan-coated PLGA containing curcumin (CH@Cur-PLGA C/SNPs). 5 mg/ml of PLGA that was solubilized in acetone (organic phase) was used, while 1% w/v pluronic-F127 was used in the aqueous phase. The PLGA solution was added with a flow rate of 1 ml/min in the aqueous solution with a phase ratio of (1:6) (organic: aqueous) in constant magnetic agitation of 500 rpm to obtain the pure nanoparticle. Similarly, the same process was done for the system of PLGA NPs containing curcumin, which were optimized with 2 mg Cur and added to the PLGA in acetone to form an organic phase. After this procedure, a nanoencapsulated system of PLGA and chitosan and the PLGA, chitosan and curcumin system were prepared. The curcumin-containing PLGA NPs obtained were then lyophilized. The authors analyzed the systems by pure curcumin Fourier transform infrared spectroscopy (FT-IR), PLGA, blank CH@PLGA C/SNPs, Cur-PLGA NPs, and C/S NPs CH@Cur-PLGA. The PLGA showed characteristic peaks at 2972.31 cm−1 for the C-H group, 1752 cm−1 for the C=O bond stretch, as well as 1082 cm−1 for the C-O-C bond stretch. The characteristic peak of CH at 1070.49 cm−1 is due to the stretching of the C=O group; 1517.98 cm−1 is attributed to the presence of stretching of the free amine group; 1668.43 cm−1 is relative to the axial vibration of the carbonyl group of acetylated amide; 3469.72 cm−1 indicates that the O-H stretch overlapped with the N-H stretch vibration. Pure curcumin exhibited characteristic peaks at 1502.55 cm−1 due to axial vibrations of the C=O and C-C bond; and a peak at 1600.92 cm−1 referring to the vibrations of the benzene ring stretch. In the case of PLGA NPs, all the characteristic PLGA peaks were present. The shell/core nanoparticles of the CH system with PLGA showed

characteristic peaks of both indicating that CH coated PLGA. In the case of Cur-PLGA NPs and shell/core nanoparticles, the characteristic Cur peaks were absent indicating that Cur could be encapsulated in PLGA NPs and CH shell/core nanoparticles with PLGA. The authors noted that the concentration of Cur also plays a significant role and has a positive effect on the release of the bioactive. The particle size and polydispersion index (PDI) of Cur-PLGA NPs increase with increasing Cur concentration in the formulation. The authors also analyzed through transmission electron microscopy (TEM) that the nanoparticles of curcumin with PLGA, and chitosan and PLGA containing curcumin showed smooth surfaces with a spherical shape, varying the size of the sphere in the range of 175-225 nm. From the results obtained in the study as: FT-IR, XRD and TEM, the authors concluded that there was a reduction in oxidative stress caused by Alzheimer's disease, an improvement in the bioavailability of the body and improvement in the antioxidant activity containing curcumin, along with stability and a reduction in toxicity.

There are several studies related to fisetin. Among these, the following articles can be cited: Sechi and Mehta (2016); Mehta et al., (2018); Vishwas et al., (2022). Sechi et al. (2016) conducted a study that aimed to formulate nanoparticles containing fisetin, which is part of the class of flavonoids. This bioactive is found in various fruits and vegetables, such as strawberries, apples, persimmons, grapes, onions, and cucumbers. To this end, it was encapsulated in polycaprolactone (PCL) and poly(d,l-lactic acid-co-glycolic acid)-poly(ethylene glycol)-block-carboxylic acid (PLGA-PEG-COOH), which are biodegradable and biocompatible polymers, having been commonly used to encapsulate hydrophobic drugs, which often have low oral bioavailability. Fisetin (FS) extracted from the leaves of a plant originally from China, was incorporated into NPs by the nanoprecipitation method. The polymers were studied in different weight ratios and FS was dissolved in 3 mL of acetonitrile. The organic solution was then added, under magnetic agitation, to an aqueous solution of Pluronic F-127 (0.1%, wt.%). The authors prepared 3 systems of solid materials for PN preparation with 5% fisetin, namely: F1 with 95% PCL; F2 with 66.5% PCL + 28.5% PLGA-PEG-COOH; and F3 with 47.5% PCL + 47.5% PLGA-PEG-COOH. The authors observed from the scanning electron microscopy (SEM) images that the NPs were well dispersed and had a well-defined spherical shape. The hydrodynamic diameters of the nanoparticles were approximately F1=146.2 nm, F2=198.7 nm, and F3=165.4 nm. In addition, no significant differences were observed for the size and morphology of the NPs in relation to the other systems with the incorporation of fisetin. The encapsulation efficiency values were expressed as approximately 82%, 75% and 70% for the F1, F2 and F3 systems, respectively. The authors further noted that in particular, PCL ensures better encapsulation due to the high affinity of hydrophobic Fs, which decreased with a progressive increase of more hydrophilic PLGA-PEG-COOH. In conclusion to this study, the authors demonstrated by the techniques of SEM, FT-IR, XRD,

encapsulation efficiency, particle size and polydispersion index, that nanocapsules containing fisetin decrease cardiovascular risks, mainly attributed to their antioxidant capacity.

In the last five years, Roy et al. (2020); El-Hussien et al. (2021); Mendez-Pfeiffer et al. (2022) conducted research on the use of chrysin as a bioactive with potential use when encapsulated. El-Hussien et al. (2021) conducted a study on the performance of chrysin, which is a flavonoid found in propolis and honey; which has several properties and among them it is a great antioxidant. This study highlighted the influence of this bioactive in the control of diseases such as diabetes mellitus and reduction of triglycerides and high-density lipoprotein cholesterol (HDL), which consequently minimizes the risks of cardiovascular diseases and stroke. The authors aimed to observe the double effect of the chrysin-containing nanocapsule for antiglycemic and antihyperlipidemic purposes. To this end, they identified that the bioactive nanoencapsulated in a polymeric matrix was successful in improving the low oral bioavailability of chrysin for the control of diabetes and hyperlipidemia. The authors used the following polymeric matrix to perform the nanoencapsulation: the DL-poly(lactic-co-/glycolic acid) copolymer (PLGA) in the proportions of 75/25 and 50/50, using acetone as solvent and *Tween* 80 as surfactant, varying the amounts of chrysin. The authors observed that the PLGA 75/25 system was better than the others used, as described in Tables 3a and 3b in the preparation of the nanocapsules, since it has a lower content of hydrophilic glycolide, suitable for the encapsulation of chrysin, which is also hydrophobic. They also observed that in relation to the efficiency of encapsulation (EE%) and bioactive carrying, the nanocapsules containing chrysin ranged from approximately 87% to 89%, due to the lipoficity of the chrysin, which allowed an effective encapsulation within the nucleus of the nanocapsules. In addition, the authors also found that the chosen preparation method allowed the loading of larger quantities of hydrophobic drug, due to the emulsification of the organic solvent with the aqueous phase in the presence of the surfactant in the nanoprecipitation technique. According to the study, the authors highlighted that the best system was composed of 50 mg of PLGA, containing 1% surfactant and 10 mg of chrysin. This result was after a standard comparison of 50 mg of PLGA, 10 mg of chrysin with codes F7, F8 and F9, which obtained the variations of 0.25%; 0,50%; and 1%, resulting respectively in the nanoparticle size at 192nm, 179nm, 176nm; polydispersion index (PDI) at 0.20, 0.20, 0.22; Zeta potential at -4.55, -5.99, -6.23; encapsulation efficiency grade at 89.67%, 85.52%, 87.10%; and controlled release in 15.68%; 17,03%; 17,41%. It was found that the particle size was approximately 176 nm and the polydispersion index was 0.22; with a Zeta potential of -6.23; encapsulation efficiency above 87% and the release of the bioactive in 17.4% for 24 hours. The authors further confirmed the size of the spherical nanoparticles, contour and nucleus using transmission electron microscopy (TEM) characterization. It was also observed by Fourier transform infrared spectroscopy (FT-IR) that the chemical interactions between chrysin and the polymer matrix. The pure chrysin spectrum showed peak at 3426.89 cm-1 due

to CH bond stretching, peaks at 1652.7 cm-1 and 1612.2 cm-1 due to C=O bond stretch, the range from 1024.98 cm-1 to 903.487 cm-1 are indicative of the axial vibrations of C-O, C-C , C-O-C bonds. The FTIR spectrum of PLGA showed characteristic absorption peaks at 3452.92 cm-1 and 1636.3 cm-1, which are due to the stretching of the OH bond and the C=O bond, respectively. The authors also observed absorption peaks at 2931.27 cm-1 and 1448.28 cm-1 due to the stretches of the C-H and C-O bonds, respectively. In the FTIR spectrum of chrysin-containing nanocapsules, absorption peaks were observed in the range of 1104.05 cm-1 to 609.396 cm-1 due to the vibrations of the chemical bonds of the chrysin groups of C-O, C-C, C-C-C, and peaks in the range of 2926.45 cm-1 to 2357.55 cm-1 attributed to the stretching of the C-H bond of chrysin. The absorption peak at 3441.35 cm-1 was assigned to terminal hydroxyl groups in the copolymer, while the ranges from 1636.3 cm-1 to 1449.24 cm-1 were assigned to C=O bonds. Therefore, all the results of the FTIR analyses corroborated the effective formation of the nanoencapsulation. Finally, the authors also carried out a comparative study of the stability and the effect of the encapsulation efficiency of the bioactive after 3 months of storage of the nanocapsule containing chrysin and this showed good stability during storage.

Among some studies in the literature between 2020 and 2022, Cordenonsi et al. (2020) and Wang et al. (2022) directed their studies to the flavanone class of bioactives. Cordenonsi et al. (2020) conducted a study describing the development and characterizations of polymeric nanoparticles loaded with narigine and narigine. These bioactives are part of the class of flavonoids with great antioxidant importance and can be found in citrus fruits such as grapefruit. The nanoparticles of narigine (NAR) and narygenin (NGE) were prepared by the nanoprecipitation technique using ethanol as solvent, the copolymer of methacrylic acid: Eudragit®L100, and surfactants: *Polysorbate* 80 and isopropyl adipate. The two separate flavonoids, Eudragit®L100 and isopropyl adipado were dissolved in ethanol (organic phase). They were then poured over the aqueous phase containing polysorbate 80 for each phase, then the solvent was removed by evaporation. The separate NAR and NGE nanoparticles were prepared in a similar way to NAR-NGE-NPs. The authors observed by transmission electron microscopy that the Eudragit®L100 nanoparticles had regular and spherical shapes. The Fourier transform infrared spectroscopy (FT-IR) analysis of the NAR and NGE spectra showed their characteristic peaks and the Eudragit®L 100 (3c) spectra showed peak absorption due to the stretching of the C=O bond of the carboxylic acid groups located at 1,700 cm-1. The range between 2,500 cm-1 to 3,500 cm-1 can be attributed to the stretch of the OH group bond. The range of 2,900 cm-1 to 3,000 cm-1 can be attributed to the stretching of the C-H link. The formation of the NAR and NGE nanoparticle with Eudragit®L100 was confirmed by this analysis. The authors further noted that no new chemical bonds were identified after the preparation of the polymer nanoparticles containing NAR-NGE, and the results confirmed that the bioactives are dispersed in the Eudragit®L100 polymer. The authors also noted that forced degradation and photodegradation stability studies are important as they indicate

chemical stability. Ultraviolet radiation (UV-C) has high energy and can be the cause of many oxidation reactions or breaking weak chemical bonds. In the forced degradation analysis, the degradation profile was caused by UV-C, revealing that NAR degraded by 12% and NGE by about 6% in 76 hours. From this analysis, the authors considered an improvement in photostability and protection against the degradation of NAR and NGE. When compared to non-encapsulated bioactives, within 48 hours there was a degradation of 50% for NAR and 60% for NGE. Based on the observed results, the authors concluded that the NAR-NGE nanoparticle was successfully developed by the nanoprecipitation technique, demonstrating the generation of a homogeneous nanoparticle with a nanometer size of 121 nm, a polydispersion index of approximately 0.10 and a zeta potential of -16.60.

Some articles have addressed studies of catechin encapsulation by the nanopreciptation method between the years 2021 and 2022. (Qi, *et al*., 2021; Han, *et al*., 2022; Jiang, *et al*., 2022). Han et al. (2022) conducted a study of the effect of encapsulation of the bioactive catechin with a concentration of 2 mM in β-cyclodextrins (β-CD). This study aimed to evaluate the conditions on the size of the nanoparticles, as well as the characterization of the physicochemical properties of the material obtained by the nanoprecipitation technique. The authors reported in their study that catechin, being a phenolic substance of the flavan class. (Arts; Hollman; Kromhout, 1999; Ho; Thoo; Young; Siow, 2017) in order to obtain better properties; among them is antioxidant activity. Cyclodextrins have been considered as simple, available, economical and effective encapsulants. The authors reported that the catechins and β-CD nanoparticles were prepared at a molar ratio of 1:1. First, β-CD was dissolved in 10 mL of water (aqueous phase), then 1 mL containing different concentrations of catechin was dripped into the aqueous solution under magnetic stirring at 200 rpm, maintained for 5 h. Characterizations were performed by reducing the solvent volume at a rate of 2 mL/min. The authors observed from the scanning electron microscopy (SEM) analysis that the β-CD nanoparticles containing catechins were spherical in shape. By the analysis of infrared spectroscopy with Fourier transform (FT-IR) for catechin (CA) it was observed that peak absorption at 3412 cm-1 is due to the stretching of the bond of the OH group. The absorption peak at 1363 $^{cm-1}$ was attributed to vibration of the OH group bonds. The characteristic peaks in the range of 1400 $^{cm-1\ to\ 1600}$ cm-1 were attributed to the stretching vibration of the C=C bond of the aromatic ring. The absorption range between 1200 $^{cm-1\ and\ 1300\ cm-1}$ was assigned to the stretches of the C-O and C-C bonds. In the β-CD spectrum, the authors identified absorption peaks characteristic of stretching the bonds of OH, C-H, H-O-H C-O, and C-O-C at 3387 cm-1, 2929 cm-1, ^{1652} cm-1, 1155 $^{cm-1,\ and\ 1028\ cm-1}$, respectively. When observing the spectrum of the nanoparticles of β-CD containing CA, no significant differences were found compared to that of the β-CD encapsulant, due to the proportion of CA being 20%. Thus, characteristic peaks were superimposed, being identified with an increase in the intensity of the stretch peaks at 1155 cm-1 $^{and\ 1029}$ cm-1. The authors further observed that there was a small redirection of the stretch peaks at 3369 cm-1 $^{and\ 2927}$ cm-1, which may

be due to intermolecular interactions by the formation of the hydrogen bonds. In the X-ray diffractogram (XRD) analysis, the standards for β-CD and β-CD containing the bioactive ingredient were presented. The authors observed that catechin showed characteristic peaks at 2(θ) at 10.3º, 12.2º, 14.7º, 16.4º, 19.4º, 23º, 24.1º and 26º, indicating a crystalline nature. The XRD standard of β-CD showed characteristic peaks of pure encapsulating material at 9º, 10.6º, 12.5º, 15.3º, 17.1º, 19.6º, 22.7º and 27º. For the standard β-CD containing the bioactive, the presence of new crystalline phases was observed, indicating the effective inclusion of the bioactive in the encapsulant structure. By monitoring the stability of β-CD nanoparticles containing catechin, it was also observed that catechin is easily oxidized when exposed to air, maintaining its antioxidant retention at approximately 16% after 30 days. While, the bioactive encapsulated with the cyclodextrin β achieved an antioxidant yield of more than 70% after 30 days, indicating the efficiency of encapsulation in protecting the bioactive. Considering the results obtained, the authors found that, when preparing the encapsulation of catechin in β-cyclodextrin, there was stability in the size of the nanoparticles and preservation of the antioxidant property of the encapsulated bioactive. As a result, the release of the bioactive occurred in a controlled manner to the desired location in the body.

Xing et al. (2022) conducted a study using the rapid nanoprecipitation technique to obtain zein nanoparticles containing resveratrol. Resveratrol is a bioactive of the polyphenol group, and is found in grapes, juices and red wines. This bioactive has great benefits for human health due to its strong antioxidant action, reducing free radicals, consequently protecting the body from inflammation and natural oxidation. However, its low bioavailability, poor water solubility, and instability affect its both nutraceutical and pharmaceutical applications. In this work a strategy employing anti-solvent nanoprecipitation and a rapid precipitation was used for the fabrication of resveratrol nanoparticles, using a mixer, which allows a rapid mixing in the order of milliseconds to generate synergistically trapped nanoparticles. Zein nanoparticles containing resveratrol (Res) were produced by the rapid nanoprecipitation technique, using the multi-inlet mixer, containing 4 syringes. The first flow was zein in an EtOH/H2O mixture (80% EtOH, v/v) at a concentration of 1.0 mg/mL, the second flow was Res in EtOH (100% v/v) and a projected volume of buffer (10 mM sodium citrate, 150 μM citric acid, pH 7.3) were placed in two syringes as the third and fourth flows. After the preparation of the nanoparticles, the discharged ethanol and resveratrol were removed by ultrafiltration at 5000 rpm for 5 min, being repeated three times. The rapid mixing of solvent and anti-solvent induces a co-precipitation of resveratrol and zein and consequently forms nanoparticles in which both are trapped. For comparison, the conventional method of anti-solvent precipitation was also adopted to prepare zein NPs containing resveratrol at the same final concentration of resveratrol and zein in solution. The authors observed that simultaneously the encapsulation capacity of the micellar structures (DLE% and DLC%) obtained by the calibration curve for the resulting NPs by the rapid nanoprecipitation method

(FNP) are about 52% and 51%, which are much higher than these values of NPs of the traditional precipitation about 18% and 26% respectively. Fourier transform infrared spectroscopy (FTIR) analysis also observed for resveratrol stretch peaks at 966 cm−1 and 987 cm−1 that indicate double transolefinic bonds of C=C. The characteristic peaks of the FTIR spectrum centered at 1153 cm−1 were assigned to the axial stretch vibrations of C-O and the peak at 1606 cm−1 was attributed to the double-bonded aromatic stretch for zein. The peak adsorption characteristic of amide II on zein is demonstrated at 1535 cm−1. Whereas these typical peaks are weakened or do not appear in the spectrum of resveratrol-containing zein nanoparticles, this be indicative of the complexity between resveratrol and zein. In addition, the encapsulation of resveratrol can also contribute to the reduction of peaks. The peak at 3190 cm−1 related to the -OH functional group of resveratrol and zein, changes to a higher number of resveratrol-containing zein nanoparticles, which indicates the overlap of the binding of the -OH groups in resveratrol and zein and further supports successful encapsulation. It was also observed the change of the characteristic peak of resveratrol from 1606 cm−1 to 1562 cm−1, which suggests the state of interaction between the bioactive and the encapsulant. The authors also evaluated the release of resveratrol and the antioxidant capacity of zein nanoparticles containing the bioactive. The cumulative release test was monitored by the ultraviolet absorption technique (UV-vis). Nanoparticles containing the bioactive show an increased release of up to 20% within 5 h, after which time no further release was observed. The effects of different factors have been explored, leading to nanoparticles loaded with the bioactive with controllable hydrodynamic radius (50-108 nm) and narrow size distribution (PDI ~ 0.1), as well as the appropriate loading capacity of the bioactive (DLC) from 30% to 57%. It was observed that encapsulation was effective due to the higher antioxidant capacity of the bioactive. The authors concluded that the control of rapid nanoprecipitation on particle formation generates products that may have applications in dietary supplements and pharmaceuticals.

6 FINAL THOUGHTS

Related studies of encapsulation and nanoencapsulation of bioactives in general have been growing rapidly in the last 5 years. Because they are a group of bioactives present in functional foods, flavonoids have a high capacity for important therapeutic action. The flavonoid content induces different properties found in certain foods, including antioxidant and antimicrobial characteristics. The functionality of flavonoid groups depends on the orientation and number of active hydroxyl (-OH) groups of each molecule, which are responsible for defending the oxidative process that happens naturally in the body. It has been seen that one of the ways to optimize the intake of these bioactives is in the form of nutraceuticals. Thus, the use of nutraceuticals as well as the consumption of functional or fortified foods play an important role both in nutrition and in the prevention or treatment of various vascular, cardiovascular, and cancer diseases, among others.

From the bibliographic survey carried out, it is noted that the efficiency of encapsulation and nanoencapsulation for the protection of the bioactive and for its controlled delivery is great. The nanoprecipitation technique proved to be a better alternative for nanoencapsulation, from different coating materials, the most common being PCL, PLGA and PLA, for bioactives obtained from the flavonoid group, as it is a low-cost method with high efficiency and good reproducibility. In addition, the technique demonstrates a lot of quality and efficiency in which it can generate great benefits to society and is very necessary because the exposure to high temperatures is considered more worrying regarding the success of the generation of a material with a longer shelf life.

REFERENCES

ABU-TAWEEL, G. M.; ATTIA, M. F.; HUSSEIN, J.; MEKAWI, E. M.; GALAL, H. M.; AHMED, E. I.; ALLAM, A. A.; EL-NAGGAR, M. E. Curcumin nanoparticles have potential antioxidant effect and restore tetrahydrobiopterin levels in experimental diabetes. Biomedicine & Pharmacotherapy. v. 131, 110688. 2020. DOI: https://doi.org/10.1016/j.biopha.2020.110688.

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA – ANVISA. Biblioteca de alimentos. 2022.

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA – ANVISA. Resolução da diretoria colegiada - RDC nº 243, de 26 de julho de 2018.

AL-FARSI, M.; AL-AMRI, A.; AL-HADHRAMI, A.; AL-BELUSHI, S. Color, flavonoids, phenolics and antioxidants of Omani honey. Heliyon. v. 4. Issue 10. 2018. DOI: https://doi.org/10.1016/j.heliyon.2018.e00874.

ALSHEHRI, M. M.; SHARIFI-RAD, J.; HERRERA-BRAVO, J.; JARA, E. L.; SALAZAR, L. A.; KREGIEL, D.; UPRETY, Y.; AKRAM, M.; IQBAL, M.; MARTORELL, M.; TORRENS-MAS, M.; CHO, W. C. Therapeutic potential of isoflavones with an emphasis on daidzein. Oxidative Medicine and Cellular Longevity, Article 6331630. 2021. DOI: https://doi.org/10.1155/ 2021/6331630.

ALZHEIMER'S DISEASE. Journal of Drug Delivery Science and Technology, v. 61, 102242. 2021. DOI: https://doi.org/10.1016/j.jddst.2020.102242.

ANJO, F. A.; SARAIVA, B. R.; OGAWA, C. Y. L.; VITAL, A.C. P.; SATO, F.; MATUMOTO-PINTRO, P. T. Phytochemical and technological characterization of canistel dehydrated pulp: a new potential food ingredien. Agrarian and Biological Sciences. v. 10 n. 1. DOI: https://doi.org/10.33448/rsd-v10i1.11577.

ARONSON, J. K. Defining "nutraceuticals": neither nutritious nor pharmaceutical. British Journal of Clinical Pharmacology, [s. l.], v. 83, n. 1, p. 8–19, 2017. DOI: 10.1111/bcp.12935.

ARTS, I.C.W.; HOLLMAN, P.C.H.; KROMHOUT, D. Chocolate as a source of tea flavonoids. The Lancet. v. 354, Issue 9177.1999. p. 488. DOI: https://doi.org/10.1016/S0140-6736(99)02267-9.

ASSOCIAÇÃO BRASILEIRA DAS EMPRESAS DE PRODUTOS NUTRICIONAIS – ABENUTRI. 2022.

ASSOCIAÇÃO BRASILEIRA DOS FRABRICANTES DE SUPLEMENTOS NUTRICIONAIS E ALIMENTOS PARA FINS ESPECIAIS – BRASNUTRI. 2022.

ASSOCIAÇÃO BRASILEIRA PARA INDÚSTRIA DE ALIMENTOS PARA FINS ESPECIAIS – ABIAD. Comportamento dos consumidores de suplementos alimentares durante a pandemia de COVID-19.

ASSOCIAÇÃO BRASILEIRA PARA INDÚSTRIA DE ALIMENTOS PARA FINS ESPECIAIS – ABIAD. Importações | em milhões de dólares e variação percentual | Janeiro a Junho 2021.

BARRETO, A. R.; MÉRIDA, L. G. R.; ETCHEPARE, M. de A.; JACOB-LOPES, E.; MENEZES, C. R. De. Coating materials used in the microencapsulation of probiotics. Ciência e Natura, Santa Maria, v. 37, n. 0, p. 164–174. 2015. DOI: 10.5902/2179460X19747.

BAYER. ASPIRINA®. 2022.

CORDENONSIA, L. M.; SPONCHIADOA, R. M; BANDEIRA, J. R.; SANTOS, R. C. V.; RAFFIN, R. P.; SCHAPOVAL, E. E. S. Polymeric nanoparticles loaded naringin and naringenin: effect of solvent, characterization, photodegradation and stability studies. Drug Analytical Research. v. 4, n. 2, p. 64-71. 2020. DOI: https://doi.org/10.22456/2527-2616.108783.

COSTA, N. M. B.; ROSA, C. O. B. Alimentos Funcionais – Componentes bioativos e efeitos fisiológicos. 2ª Ed. revisada e ampliada. Editor Rubio Ltda. 2016. p. 61-78.
COWAN, M.M. Plant Products as Antimicrobial Agents. Clinical Microbiology Reviews. American Society for Microbiology, v. 12, Issue 4, p. 562 – 584. DOI: https://doi.org/10.1128/CMR.12.4.564.

CUSHNIE, T., LAMB, A.J. Antimicrobial activity of flavonoids. International Journal of Antimicrobial Agents, v. 26, issue 5, p. 343 – 356. 2005. DOI: https://doi.org/10.1016/j.ijantimicag.2005.09.002.

DE VOS, P.; FAAS, M. M.; SPASOJEVIC, M.; SIKKEMA, J. Encapsulation for preservation of functionality and targeted delivery of bioactive food components. International Dairy Journal, [*S.l.*], v. 20, n.4, p. 292–302. 2010. DOI: https://doi.org/10.1016/j.idairyj.2009.11.008.

DHAS, N.; MEHTA, T. Intranasal delivery of chitosan decorated PLGA core /shell nanoparticles containing flavonoid to reduce oxidative stress in the treatment of
DUBEY, R.; SHAMI, T. C.; BHASKER RAO, K.U. Microencapsulation Technology and Applications. Defence Science Journal, [*s. l.*], v. 59, n. 1, p. 82–95, 2009. DOI: 10.14429/dsj.59.1489.

EL-HUSSIEN, D; EL-ZAAFARANY, G. M.; NASR, M.; SAMMOUR, O. Chrysin nanocapsules with dual anti-glycemic and anti-hyperlipidemic effects: Chemometric optimization, physicochemical characterization and pharmacodynamic assessment. International Journal of Pharmaceutics, v. 592, 120044. 2021. DOI: https://doi.org/10.1016/j.ijpharm.2020.120044.

ELIK, A.; YANIK, D. K.; GÖĞÜŞ, F. A comparative study of encapsulation of carotenoid enriched-flaxseed oil and flaxseed oil by spray freeze-drying and spray drying techniques. LWT. v. 143, 111153. 2021. DOI: https://doi.org/10.1016/j.lwt.2021.111153.

FELTRIN, F. S.; AGNER, T.; SAYER, C.; LONA, L. M. F. Curcumin encapsulation in functional PLGA nanoparticles: A promising strategy for cancer therapies. Advances in Colloid and Interface Science. v. 300, 102582. 2022. Doi: https://doi.org/10.1016/j.cis.2021.102582.

FESSI, H.; PUISIEUX, F.; DEVISSAGUET, J. P.; AMMOURY, N.; BENITA, S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. International Journal of Pharmaceutics. v. 55, Issue 1, 1989, p. R1-R4. DOI: https://doi.org/10.1016/0378-5173(89)90281-0.

FRUTOS, M. J., RINCON-FRUTOS, ´ L., & VALERO-CASES, E. Chapter 2.14 - Rutin. Nonvitamin and nonmineral nutritional supplements, Academic Press. DOI: 10.1016/B978-0-12-812491-8.00015-1. 2019. p. 111–117.
FRUTOS, M. J.; RINCON-FRUTOS, L.; VALERO-CASES, E. Chapter 2.14 - Rutin. Nonvitamin and nonmineral nutritional supplements. Academic Press. 2019. p. 111-117. DOI: 10.1016/B978-0-12-812491-8.00015-1.

GANGURDE, A. B.; ALI, M. T.; PAWAR, J. N.; AMIN, P. D. Encapsulation of vitamin E acetate to convert oil to powder microcapsule using different starch derivatives. Journal of Pharmaceutical Investigation, [*S.l.*], v. 47, n. 6, p. 559–574. 2016. DOI:10.1007/s40005-016-0287-3/2016.

GODSWILLAWUCHI, C.; MORYA, S.; DENDEGH, T. A.; ODILICHUKWU-R, C.; OKPALA; KORZENIOWSKA, M. Nanoencapsulation of food bioactive constituents and its associated processes: A revisit. Bioresource Technology Reports, v. 19, 101088. 2022. DOI: https://doi.org/10.1016/j.biteb.2022.101088.

GOVERNO DO BRASIL – GOV-BR. Ministério da Agricultura, Pecuária e Abastecimento. DECRETO-LEI Nº 986, DE 21 DE OUTUBRO DE1969. Institui Normas Básicas Sobre Alimentos. 1969.

HAN, Y.; JIA, F.; BAI, S.; XIAO, Y.; MENG, X.; JIANG, L. Effect of operating conditions on size of catechin/β-cyclodextrin nanoparticles prepared by nanoprecipitation and characterization of their physicochemical properties. LWT, v. 153, 112447. 2022. DOI: https://doi.org/10.1016/j.lwt.2021.112447.

HASLER, C. M. Functional foods: their role in disease prevention and health promotion. Food Technology, v. 52, Issue 2, p. 57-62. 1998.

HE, H. F.; WEI, K.; YIN, J.; YE, Y. Insight into tea flavonoids: composition and chemistry. Food Reviews International, v. 37, Issue 8, p. 812–823. 2020. DOI: https://doi.org/10.1080/87559129.2020.1721530.

HO, S.; THOO, Y. Y.; YOUNG, D. J.; SIOW, L. F. Inclusion complexation of catechin by β-cyclodextrins: Characterization and storage stability. LWT. v. 86. 2017. p. 555-565. Doi: https://doi.org/10.1016/j.lwt.2017.08.041.

JIANG, L.; WANG, F.; DU, M.; XIE, C.; XIE, X; ZHANG, H.; MENG, X.; LI, A.; DENG, T. Encapsulation of catechin into nano-cyclodextrin-metal-organic frameworks: Preparation, characterization, and evaluation of storage stability and bioavailability. Food Chemistry, v. 394, 133553. 2022. DOI: https://doi.org/10.1016/j.foodchem.2022.133553.

KAUSHAL, N.; SINGH, M.; SANGWAN, R. S. Flavonoids: Food associations, therapeutic mechanisms, metabolism and nanoformulations. Food Research International. v. 157, 2022. DOI: https://doi.org/10.1016/j.foodres.2022.111442.

KHANA, N.; AMEEDUZZAFAR; KHANNA, K.; BHATNAGAR, A.; AHMADA, F. J.; ALI, A. Chitosan coated PLGA nanoparticles amplify the ocular hypotensive effect of forskolin: Statistical design, characterization and in vivo studies. International Journal of Biological Macromolecules. v. 116, p. 648-663. 2018. DOI: https://doi.org/10.1016/j.ijbiomac.2018.04.122.

KOOP, B. L.; SILVA, M. N.; SILVA, F. D.; LIMA, K. T. S.; SOARES, L. S.; ANDRADE, C. J.; VALENCIA, G. A.; MONTEIRO, A. R. Flavonoids, anthocyanins, betalains, curcumin, and carotenoids: Sources, classification and enhanced stabilization by encapsulation and adsorption. Food Research International, v. 153, 110929. 2022. DOI: https://doi.org/10.1016/j.foodres.2021.110929.

LEPELTIER, E.; BOURGAUX, C.; COUVREUR, P. Nanoprecipitation and the “Ouzo effect”: Application to drug delivery devices. Advanced Drug Delivery Reviews, [*S.l.*], v. 71, p. 86-97. 2014. DOI: 10.1016/j.addr.2013.12.009.

LI, S., ZHANG, L., WAN, X., ZHAN, J., & HO, C. T. Focusing on the recent progress of tea polyphenol chemistry and perspectives. Food Science and Human Wellness, vol. 11, Issue 3, p. 437–444. 2022. DOI: https://doi.org/10.1016/j.fshw.2021.12.033.

LIU, Y.; LIU, L. Nutraceuticals Definition, Kinds and Applications. *In*: LIU, L.; CHEN, J. (Eds.). Systems and Synthetic Biotechnology for Production of Nutraceuticals. 1. ed. Singapore: Springer, 2019. p. 1–7.

MEHTA, P.; PAWAR, A.; MAHADIK, K.; BOTHIRAJA, C. Emerging novel drug delivery strategies for bioactive flavonol fisetin in Biomedicine. Biomedicine & Pharmacotherapy. v. 106, p. 1282-1291. 2018. DOI: https://doi.org/10.1016/j.biopha.2018.07.079.

MENDEZ-PFEIFFER, P.; JUAREZ, J.; HERNANDEZ, J.; TABOADA, P.; VIRU´ES, C.; ALDAY, E.; VALENCIA, D.; VELAZQUEZ, C. Polymeric nanoparticles for the delivery of Sonoran desert propolis: Synthesis, characterization and antiproliferative activity on cancer cells. Colloids and Surfaces B: Biointerfaces, v. 215, 112475. 2022. DOI: https://doi.org/10.1016/j.colsurfb.2022.112475.

MILADI, K.; SFAR, S.; FESSI, H.; ELAISSARI, A. Nanoprecipitation Process: From Particle Preparation to In Vivo Applications. C. Vauthier, G. Ponchel (Eds.), Polymer Nanoparticles for Nanomedicines. Springer International Publishing, pp. 17-53. 2016.

MINETTI, F.; MENGATTO, L. N.; OLIVARES, M. L.; BERLI, C. L. A. Generation of curcumin-loaded albumin nanoparticles by using off-the-shelf microfluidics driven by gravity. Food Research International. v. 162, part A, 111984. 2022. DOI: https://doi.org/10.1016/j.foodres.2022.111984.

MUTUKURI, T. T.; WILSON, N. E.; TAYLOR, L. S.; TOPP. E. M.;ZHOU, Q. T. Effects of drying method and excipient on the structure and physical stability of protein solids: Freeze drying vs. spray freeze drying. International Journal of Pharmaceutics. v. 594, 120169. 2021. DOI: https://doi.org/10.1016/j.ijpharm.2020.120169.

NAZLI, E.; SAFIYE, A.; EREM, B. Nanocapsules for Drug Delivery: An Updated Review of the Last Decade. Recent Patents on Drug Delivery & Formulation. Bentham Science Publishers. v. 12, n. 4, p. 252-266. 2018. DOI: https://doi.org/10.2174/1872211313666190123153711.

NESTERENKO, A.; ALRIC, I.; SILVESTRE, F.; DURRIEU, V. Vegetable proteins in microencapsulation: A review of recent interventions and their effectiveness. Industrial Crops and Products, [*s. l.*], v. 42, p. 469–479, 2013. DOI: 10.1016/j.indcrop.2012.06.035.

NEVES, M. I. L.; DESOBRY-BANON, S.; PERRONE, I. T.; DESOBRY, S.; PETIT, J. Encapsulation of curcumin in milk powders by spray-drying: Physicochemistry, rehydration properties, and stability during storage. Powder Technology. v. 345, p. 601-607. 2019. DOI: https://doi.org/10.1016/j.powtec.2019.01.049.

ORLIKOVA, B., TASDEMIR, D., GOLAIS, F., DICATO, M., & DIEDERICH, M. Dietary chalcones with chemopreventive and chemotherapeutic potential. Genes and Nutrition, v. 6, p. 125–147. 2011. DOI: https://doi.org/10.1007/s12263-011-0210-5.

PEREIRA, K. C.; FERREIRA, D. C. M.; ALVARENGA, G. F.; PEREIRA, M. S. S.; BARCELOS, M. C. S.; COSTA, J. M. G. Da. Microencapsulation and release controlled by the diffusion of food ingredients produced by spray drying: a review. Brazilian Journal of Food Technology, Campinas, vol. 21, n. e2017083. 2018. DOI: 10.1590/1981-6723.08317.

QI, Y.; LI, J.; NIE, Q.; GAO, G.; YANG, Q.; LI, Z.; LI, Q.; HAN, S.; DING, J.; LI, Y.; ZHANG, J. Polyphenol-assisted facile assembly of bioactive nanoparticles for targeted therapy of heart diseases. Biomaterials, v. 275, 120952. 2021. DOI: https://doi.org/10.1016/j.biomaterials.2021.120952.

REBELO, R.; FERNANDES, M.; FANGUEIRO, R. Biopolymers in Medical Implants: A Brief Review. Procedia Engineering, [*s. l.*], v. 200, p. 236–243. 2017. DOI: 10.1016/j.proeng.2017.07.034.

REZA, T.; KRISTEN, E. M.; JACEK, J. Fish protein isolate: Development of functional foods with nutraceutical ingredients. Journal of functional foods, [*S.l.*], v. 18, Part A, p. 746-756. 2015. DOI: https://doi.org/10.1016/j.jff.2014.05.006.

RIVAS, C. J. M.; TARHINI, M.; BADRI, W.; MILADI, K.; GREIGE-GERGES, H.; NAZARI, Q. A.; RODRÍGUEZ, S. A. G; ROMÁN, R. A.; FESSI, H.; ELAISSARI, A. Nanoprecipitation process: From encapsulation to drug delivery. International Journal of Pharmaceutics, v. 532, Edição 1, p. 66-81. 2017. DOI: https://doi.org/10.1016/j.ijpharm.2017.08.064.

RODRÍGUEZ, J.; MARTÍN, M. J.; RUIZ, M. A.; CLARES, B. Current encapsulation strategies for bioactive oils: From alimentary to pharmaceutical perspectives. Food Research International, [*S.l.*], v. 83, p. 41–59. 2016. DOI: https://doi.org/10.1016/j.foodres.2016.01.032.

ROMÁN, G. C.; JACKSON, R. E.; GADHIA; R.; ROMÁN, A. N.; REIS, J. Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Revue Neurologique. v. 175, Issue 10, p. 724-741. 2019. DOI: https://doi.org/10.1016/j.neurol.2019.08.005.

ROMANI, a.; CAMPO, M.; URCIUOLI, S.; MARRONE, G.; NOCE, A.; BERNINI, R. An Industrial and Sustainable Platform for the Production of Bioactive Micronized Powders and Extracts Enriched in Polyphenols From *Olea europaea L.* and *Vitis vinifera L.* Wastes. Sec. Nutrition and Food Science Technology. 2020. DOI: https://doi.org/10.3389/fnut.2020.00120.

ROSALES, T. K. O.; SILVA, M. P.; LOURENÇO, F. R.; HASSIMOTTO, N. M. A.; FABI, J. P. Nanoencapsulation of anthocyanins from blackberry (Rubus spp.) through pectin and lysozyme self-assembling. Food Hydrocolloids, v. 114, 106563. 2021. DOI: https://doi.org/10.1016/j.foodhyd.2020.106563.

ROY, S.; MANNA, K.; JHA, T.; SAHA, K. D. Chrysin-loaded PLGA attenuates OVA-induced allergic asthma by modulating TLR/NF-κB/NLRP3 axis. Nanomedicine: Nanotechnology, Biology, and Medicine, v. 30, 102292. 2020. DOI: 10.1016/j.nano.2020.102292.

SAIFULLAH, Md.; SHISHIR, M. R. I.; FERDOWSI, R.; TANVER RAHMAN, M. R.; VAN VUONG, Q. Micro and nano encapsulation, retention and controlled release of flavor and aroma compounds: A critical review. Trends in Food Science & Technology, v. 86, p. 230–251. 2019. DOI: 10.1016/j.tifs.2019.02.030.

SECHI, M.; DEEBA, D. N. SYED; PALA, N.; MARIANI, A.; MARCEDDU, S.; BRUNETTI, A.; MUKHTAR, H.; SANNA, V. Nanoencapsulation of dietary flavonoid fisetin: Formulation and *in vitro* antioxidant and α-glucosidase inhibition activities. Materials Science and Engineering: C, v 68, p 594-602. 2016 DOI: http://dx.doi.org/10.1016/j.msec.2016.06.042.

SHISHIR, M. R. I.; XIE, L.; SUN, C.; ZHENG, X.; CHEN, W. Advances in micro and nano-encapsulation of bioactive compounds using biopolymer and lipid-based transporters. Trends in Food Science & Technology, v. 78, p. 34–60. 2018. DOI: 10.1016/j.tifs.2018.05.018.

SIES, H. Findings in redox biology: From H_2O_2 to oxidative stress. J Biol Chem REFLECTIONS, v 295, 39, p. 13458-13473. 2020. DOI: 10.1074/jbc.X120.015651.

SILVA, P. T. Da; FRIES, L. L. M.; MENEZES, C. R. De; HOLKEM, A. T.; SCHWAN, C. L.; WIGMANN, É. F.; BASTOS, J. de O.; SILVA, C. de B. Da; SILVA, P. T. Da; FRIES, L. L. M.; MENEZES, C. R. De; HOLKEM, A. T.; SCHWAN, C. L.; WIGMANN, É. F.; BASTOS, J. de O.; SILVA, C. de B. Da. Microencapsulation: concepts, mechanisms, methods and some applications in food technology. Food Technology. Ciência Rural, Santa Maria, v. 44, n. 7, p. 1304–1311. 2014. DOI: 10.1590/0103-8478cr20130971.

SILVA, T. M.; RODRIGUES, L. Z.; NUNES, G. L.; CODEVILLA, C. F.; SILVA, C. B.; MENEZES, C. R. Encapsulação de Compostos Bioativos por Coacervação Complexa. Ciência e Natura, [*S.l.*], v. 37, p. 56– 64. 2015. DOI:10.5902/2179- 460X19715.

SIMÕES, L. de S.; MADALENA, D. A.; PINHEIRO, A. C.; TEIXEIRA, J. A.; VICENTE, A. A.; RAMOS, Ó. L. Micro- and nano bio-based delivery systems for food applications: In vitro behavior. Advances in Colloid and Interface Science, [*s. l.*], Vol. 243, p. 23–45. 2017. DOI: 10.1016/j.cis.2017.02.010.

SOUZA, V. B.; THOMAZINI, M.; CHAVES, I. E.; FERRO-FURTADO, R.; FAVARO-TRINDADE, C. S. Microencapsulation by complex coacervation as a tool to protect bioactive compounds and to reduce astringency and strong flavor of vegetable extracts. Food Hydrocolloids. v. 98, 105244. 2020. DOI: https://doi.org/10.1016/j.foodhyd.2019.105244.

TAVARES, M, R. O efeito da concentração da policaprolactona no desenvolvimento de nanopartículas poliméricas visando a transposição dos fármacos através da barreira hematoencefálica. 2016. Dissertação. (Mestrado em Ciência e Tecnologia de Polímeros) - Instituto de Macromoléculas Professora Eloisa Mano. Universidade Federal do Rio de Janeiro. 2016. p. 53-56.

VISHWAS, S.; SINGH, S. K.; GULATI, M.; AWASTHI, A.; KHURSHEED, R.; CORRIE, L.; KUMAR, R.; COLLET, T.; LOEBENBERG, R.; PORWAL, O.; GUPTA, S.; JHA, N. K., GUPTA, P. K.; DEVKOTA, H. P.; CHELLAPPAN, D. K.; GUPTA, G.; ADAMS, J.; DUA, K. Harnessing the therapeutic potential of fisetin and its nanoparticles: Journey so far and road ahead. Chemico-Biological Interactions. v. 356, 109869. 2022. DOI: https://doi.org/10.1016/j.cbi.2022.109869.

WANG, S.; XUE, T.; NIU, B.; WEI, L.; WANG, H. Preparation, characterization and antibacterial property of naringin loaded PLGA nanospheres. Progress in Natural Science: Materials International, v. 32, Issue 4, p. 498-503. 2022. DOI: https://doi.org/10.1016/j.pnsc.2022.08.001.

XIE, F.; POLLET, E.; HALLEY, P. J.; AVÉROUS, L. Starch-based nano-biocomposites. Progress in Polymer Science. v. 38, p. 1590-1628. 2013. DOI: 10.1016/j.progpolymsci.2013.05.002.

XING, M.; ZHAO, H.;AHMEDA, R.; WANGA, X.; LIU, J.;WANGA, J.; GUO, A. WANG, M. Fabrication of resveratrol-loaded zein nanoparticles based on flash nanoprecipitation. Colloids and Surfaces A: Physicochemical and Engineering Aspects, v, 654. 129829. 2022. DOI: https://doi.org/10.1016/j.colsurfa.2022.129829.

ZAKIR, M. M.; FREITAS, I. R. Benefícios à saúde humana do consumo de isoflavonas presentes em produtos derivados da soja. Journal of Bioenergy and Food Science, [*S.l.*], v. 2, n. 3, p. 107-116. 2015. DOI: http://dx.doi.org/10.18067/jbfs.v2i3.50.

ZANONI, F.; PRIMITERRA, M.; ANGELI, N.; ZOCCATELLI, G. Microencapsulation by spray-drying of polyphenols extracted from red chicory and red cabbage: Effects on stability and color properties. Food Chemistry. v. 307, 125535. 2020. DOI: https://doi.org/10.1016/j.foodchem.2019.125535.