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FOOD TECHNOLOGY

Chrysin flavonoid encapsulation: a review about methodologies used and biological potential

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ABSTRACT: Chrysin flavonoid has been presented as having numerous and promising bioactive effects, such as antioxidant, anticonvulsant, antihypertensive, anti-inflammatory, antineoplastic, antihyperlipidemic, and antidepressant. However, one of the main challenges for advances in studies on the bioactivity of chrysin is its low bioavailability in humans. Thus, aiming to overcome this barrier, several studies have demonstrated the bioactive potential of capsules containing chrysin. The objective of this review was to present the main methodologies used for the encapsulation of chrysin, and its main biological effects demonstrated so far. Our intention is to offer ways to advancement of research in the area of flavonoid encapsulation. As for the encapsulation techniques, it was found that they are diverse, and the most recurrent encapsulating agents were PEG, PLGA polymers and their derivatives, in addition to other agents, such as PCL, albumin, lipids and chitosan.The bioactive effects of the capsules are also numerous, and anticarcinogenic effects are the most frequent, in addition to other effects such as antioxidant, antidiabetic, antimicrobial and neuroprotective. In conclusion, we verified a lack of use of green techniques for the encapsulation of chrysin, and the production of lipid-water emulsions and the dissolution of chrysin in ethanol seems to be alternatives in this regard. In addition, bioactive potential of these capsules can be evaluated in other experimental models, and should advance to clinical trials and application in food formulations.
Key words: Anticarcinogenic, nanocapsules, bioavailability, PEG-PLGA.

Encapsulação do flavonoide crisina: uma revisão sobre as metodologias utilizadas e potencial biológico

RESUMO: O flavonoide crisina tem sido apresentado como tendo numerosos e promissores efeitos bioativos, como antioxidante, anticonvulsivante, anti-hipertensivo, anti-inflamatório, antineoplásico, anti-hiperlipidêmico e antidepressivo. No entanto, um dos principais desafios para o avanço dos estudos sobre a bioatividade da crisina é sua baixa biodisponibilidade em humanos. Assim, visando superar essa barreira, diversos estudos têm demonstrado o potencial bioativo de cápsulas contendo crisina. O objetivo desta revisão é apresentar as principais metodologias utilizadas para o encapsulamento da crisina e seus principais efeitos biológicos demonstrados até o momento. Nossa intenção é oferecer caminhos para o avanço das pesquisas na área de encapsulação de flavonoides. Quanto às técnicas de encapsulamento, verificou-se que são diversas, e os agentes encapsulantes mais recorrentes são os polímeros PEG, PLGA e seus derivados, além de outros agentes como PCL, albumina, lipídeos e quitosana. Os efeitos bioativos das cápsulas também são numerosos, sendo os efeitos anticarcinogênicos os mais frequentes, além de outros efeitos como antioxidante, antidiabético, antimicrobiano e neuroprotetor. Em conclusão, verificamos a falta de utilização de técnicas verdes para o encapsulamento de crisina, e a produção de emulsões lipídeo-água e dissolução da crisina em etanol parecem ser alternativas neste aspecto. Além disso, o potencial bioativo destas cápsulas pode ainda ser avaliado em outros modelos experimentais, e deve-se avançar para ensaios clínicos e aplicação em formulações alimentícias.
Palavras-chave: anticarcinogênico, nanocápsulas, biodisponibilidade, PEG-PLGA.

INTRODUCTION

Chrysin (5,7-Dihydroxyflavone) belongs to the flavone class of flavonoids, and is found naturally in honey, propolis, and several species of plants, including species of the genus *Pelargonium, Passiflora*, and the family Pinaceae (NABAVI et al., 2015). Chrysin has already been presented as having numerous and promising bioactive effects, such as antioxidant activity (PUSHPAVALLI et al., 2010), anticonvulsant (MEDINA et al., 1990), antihypertensive (VILLAR et al., 2002), anti-inflammatory (BAE et al., 2011), antineoplastic (PICHICHERO et al., 2011), antihyperlipidemic (ZARZECKI et al., 2014), and antidepressant (BORGES FILHO et al. 2015; 2016a; 2016b).

One of the main challenges for advances in studies on the bioactivity of the chrysin flavonoid is its low bioavailability in humans. Studies showed that chrysin is poorly solubilized, poorly absorbed, quickly

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metabolized and quickly eliminated in the human body, and it is estimated that its oral bioavailability is in the range of 0.003-0.02% (WALLE et al., 2001; JUNG et al., 2016; TALEBI et al., 2021).

An important way to overcome the low bioavailability of chrysin and phenolic compounds in general is the use of encapsulation techniques (KHALIB et al., 2022). So, several studies have demonstrated the development of capsules containing chrysin, and bioactive potential of these capsules. There are numerous methodologies used to produce the capsules, as well as a diversity of effects in different experimental models.

Thus, the objective of this review is to present the main methodologies used for the encapsulation of chrysin, and its main biological effects demonstrated so far. Our perspective is to offer information and alternatives for researchers who study ways to increase the bioavailability of chrysin and other flavonoids, and explore its bioactive potential. For this, we intend to describe and evaluate the methodologies and bioactivity studies presented so far, pointing out the most recurrent materials and techniques and discussing possible advances to be made in this area.

METHODOLOGY

The search was carried on the "science direct" platform, in the advanced search field. In the "title" field, the word "chrysin" was typed and in the "title, abstract or author-specified keywords" field, "nano" or "encapsulation" or "nanocapsules" words were typed.

In the search with "nano", 6 articles were found, being 6 associated with this review. In the search with "encapsulation", 9 papers were found, being 9 associated with this review. However, out of 9, 3 were also found in the first search. In the search with "nanocapsules", 2 papers associated with this review were found, but 1 had already appeared in other searches.

Thus, 13 articles of science direct platform were thoroughly evaluated for this review.

The "scopus" platform was also used for research. In the "article title, abstract, keywords" field, "chrysin nano" was used for research selecting the "article" filter. In this search, 27 articles were found, 19 of which are associated with the theme of this review. Among these 19, 6 appeared in searches on the science direct platform. Thus, scopus platform added 13 articles to this review.

Finally, "PubMed" platform was also used for research. In the "Search" field, "chrysin encapsulation" was used for research. In this search, 42 articles were found, 34 of which are associated with the theme of this review. Among these 34, 16 were not found in previous searches and were evaluated in the review.

For the preparation of this review, the encapsulation methodologies and the biological potential were evaluated separately, and are arranged this way in the article. As this is an area that has only recent studies, we did not limit the search period.

RESULTS AND DISCUSSION

Encapsulation methods

KHALID & NASEEM (2022), dissolved chrysin in organic phases which were acetone and dichloromethane (DCM). The solution was then emulsified with aqueous solution of polyvinyl alcohol (PVA) (used as surface stabilizer) by sonication and stirred over a magnetic stirrer at room temperature for 6, 7h. This is followed by centrifugation at 10,000 rpm for 30min. Supernatant was discarded and the synthesized nanoparticles were obtained as pellet, dried in hot air oven and stored.

In the EATEMADI et al. (2016) study, 20 mg chrysin and 200 mg of ε-caprolacton-poly-ethylene-glycol)-ε-caprolacton (PCL-PEG-PCL) triblock copolymers were added to DCM solvent. The mixture was added dropwise into 20 mL of H_2O. A probe-type sonicator at 80 W was used. The solution was sonicated at 16 interval and the one-minute pulse was turned off for 1s at 15s interval. For solvent evaporation and micelles formation, the beaker was opened to air during the night and in rotary evaporator the residual solvent was evaporated. For PCL-PEG-PCL synthesis, PEG and ε-caprolacton was the initiator in the presence of stannous octoate (Sn(Oct)2) as catalyst. Briefly, by utilizing mPEG, polymerization of ε-caprolacton was initiated. 3G ethylene glycol and 7.4g ε-caprolacton was added to a dry three-necked flask and under vacuum for 10min which was heated at 130 °C to dissolve the materials and remove moisture. By this mean, Sn (Oct) 2 were added into three-necked flask under a nitrogen atmosphere. A heating device was used to heat the compounds at 180 °C under stirring condition for 6h. After 12h cooling at room temperature, a firm and milky mixture was obtained. DCM was used for dissolving the mixture. After 30min, cold diethyl ether was added under stirring condition for purification. After 24h the solution was precipitated. The precipitate was stored in a desiccator.

JABBARI et al. (2018) presented doxorubicin and chrysin combination with novel

pH-responsive poly [(lactide-co-glycolic acid)-block-methacrylic acid] (PLGA-co-PMAA) nanoparticle. For this, 200 mg of PLGA-co-PMAA copolymer was dissolved in dimethyl sulfoxide (DMSO) (4 mL) under stirring at room temperature. Then, doxorubicin solution (10 mg) added to the mixture of the flask and after stirring for 24 h under dark conditions, chrysin solution (10 mg dissolved in 2 mL DMSO) was added to dozorubicin /(PLGA-co-PMAA) copolymer mixture and dispersed with the aid of ultra-sonication for 5 min. The PVA (1 wt %) solution was added dropwise (with the rate of 1 drop per 6 s) to vigorously stirring polymer/drug solution. Doxorubicin/chrysin-loaded PLGA-co-PMAA nanoparticles were collected from unloaded drugs and organic solvent using the Amicon centrifugal filters at 5000 rpm for 15 min. Drug-loaded nanoparticles were washed twice with distilled water and centrifuged at the same condition to remove any trace of the organic solvent or unbounded drugs.

FIROUZI-AMANDI et al. (2018) showed chrysin-encapsulated PLGA-PEG. PLGA-PEG tri-block copolymer was synthesized through ring opening polymerization of DL-lactide and glycolide in presence of PEG6000. PEG6000 and PLGA were copolymerized under vacuum using Sn(Oct)2 as the catalyst. The combination of DL-lactide (2.882 g), PEG6000 (1.44 g) and glycolide (0. 270 g) was completely melted in bottleneck flask in 140 °C under a nitrogen atmosphere. Then, 0.05% (w/w) Sn(Oct)2 was added and the temperature of the reaction mixture was raised to 180 °C for 5 h. The produced copolymer was dissolved in DCM and precipitated in ice-cold diethyl ether. Chrysin-loaded PLGA-PEG nanocapsule was obtained using oil-in-water (O/W) emulsion-solvent evaporation technique. Briefly, 200 mg of PLGA-PEG dissolved in 5 mL of DCM-methanol co-z solvent (4:1) and 2 mg of chrysin were moved to a centrifuge tube, and the solution mixture was gently stirred for 15 min at room temperature and emulsified using sonication in 50 mL of PVA aqueous solution (0.5%, w/v). After vacuum vaporization of the solvent, the nanocapsules were gathered by centrifugation at 12,000 rpm for 10 min at room temperature and washed three times using dH_2O. The obtained nanocapsules loaded suspensions were lyophilized and stored at 4 °C until further use. In addition, MOHAMMADIAN et al. (2016a, 2016b) also developed and evaluated bioactive potential of chrysin-PLGA-PEG nanoparticles in gastric cancer cell lines. KHALEDI et al. (2020) also showed the preparation and characterization of PLGA-PEG-PLGA polymeric nanoparticles for co-delivery of 5-fluorouracil and chrysin.

EL-HUSSIEN et al. (2021) prepared polymeric chrysin nanocapsules based on polylactic-glycolic acid PLGA. In this research, organic phase of the system composed of PLGA in different amounts, chrysin, Labrafac PG (propylene glycol dicaprylocaprate EP/propylene glycol dicaprylate/ dicaprate NF) and phosphatidylcholine was dissolved in 10mL acetone. The organic phase was added drop-wise to an aqueous solution of tween 80 as a stabilizer (20mL), placed on a magnetic stirrer at room temperature to aid the evaporation of the organic solvent.

GIACOMELI et al. (2020) investigated the effects of chrysin loaded lipid-core nanocapsules. In the methodology, loaded lipid-core nanocapsules suspensions were prepared by interfacial deposition of polymer. An organic phase containing chrysin (0.005 g), poly (ε-caprolactone) (0.100 g), pomegranate oil (0.33 mL), and sorbitan monostearate (0.077 g) were dissolved in acetone (27 mL) at 40 °C. In a separate flask, P80 (0.077 g) was added to 53 mL of water (Aqueous phase). Organic solution was poured into the aqueous phase under magnetic stirring at room temperature. After 10 min, a rotary evaporator was used to remove acetone and the suspensions were concentrated under reduced pressure. The final volume was adjusted to 10 mL for a drug concentration of 0.5 $mg.ml^{-1}$.

FERRADO et al. (2019) presented formation and characterization of self-assembled bovine serum albumin nanoparticles (BSAnp) as chrysin delivery systems. Chrysin-loaded BSAnp (BSAnp-Chrys) formation was monitored by intrinsic and extrinsic fluorescence measurements. Forthis, both native BSA and BSAnp solutions were diluted to a final concentration of 0.01%wt. in PBS buffer at pH 7.4. Chrys stock solution (2 mM) was prepared by dissolving the compound in DMSO. To perform intrinsic fluorescence binding experiments a volume of 2.0 ml containing 0.01%wt. BSA in phosphate buffered saline (PBS) was titrated by successive additions of Chrys stock solution until to reach a final concentration in the range of 0–140 μM. After Chrys addition, tubes were vigorously stirred. DMSO was chosen as solvent for binding experiments due to its properties: it is an organic solvent, water miscible, nontoxic, and widely used in biologic assays (acompound that precipitates in DMSO is a compound that cannot be biologically tested). Since it was reported that a final concentration of 10% v/v produces structural changes on BSA, it was contemplated that DMSO final concentration must not exceed 2.5%. In order to evaluate possible changes of BSA structure in presence of DMSO, a

control sample was prepared by adding a volume of 50 µl of DMSO to 2.0 ml of BSA solution (0.01% wt.). It represents the maximal concentration of DMSO used in all experiments. Intrinsic fluorescence emission spectra were recorded in triplicate at room temperature (25 °C). Finally, in order to know the mode in which chrysin is bond to BSAnp, extrinsic fluorescence measurements were performed.

ZHU et al. (2016) showed inclusion of chrysin in β-cyclodextrin complex. In this paper, an amount of recrystallizated β-cyclodextrin was completely dissolved in H_2O in accordance with the rule of 1g β-cyclodextrin adding 25mL dH_2O, and then added a certain amount of chrysin ethanol solution in some time with continuous stirring and by maintaining the temperature. The suspension was then slowly cooled at room temperature, the crystallization process was perfected in refrigerator over night, and the complex crystals were filtered in vacuum, dried at room temperature and weighed. Similarly, CHAKRABORTY et al. (2010) and SUNDARARAJAN et al. (2017) also showed inclusion of chrysin in β-cyclodextrin capsules. CHAKRABORTY et al. (2010) demonstrated antioxidant potencial, while SUNDARARAJAN et al. (2017) evaluated antioxidant and antitumorous effect *in vitro*.

RASOULI et al. (2020) developed electrospun nanofiber-mediated codelivery of curcumin andchrysin. First, PLGA/PEG copolymers were synthesized through ring-opening polymerization procedure. For fabrication of drug-loaded electrospun nanofibers (NFs), PLGA/PEG copolymers were dissolved in DCM: Methanol at a ratio of 4:1 (v/v) to prepare a 10%w/v solution. Gel permeation chromatography was used to determine the number of molecular weight (Mn) and polydispersity index (PDI) of the copolymer. To obtain drug-loaded PLGA/PEG solutions, different weight ratios of curcumin and chrysin (5:0, 10:0, 0:5, 0:10, 5:10, 5:5 and 10:5 wt:wt%, respectively, with respect to the PLGA/PEG content) were added to PLGA/PEG solution and stirred magnetically for 8h at 25 °C. The obtained solutions were fed in a 5mL plastic syringe with a blunted 22-gauge needle, and the flow rate of solution maintained at 2ml/h. The electrospun NFs were collected by a foil□coated rotating collector. The electrospinning was carried out at a range of 22–25kV and needle-to-collector distance of 200mm. The gained NFs were dried for 24h under vacuum oven to remove the residual solvent. Similarly, BAGHERI et al. (2018), TAVAKOLI et al. (2018) and LOFTI-ATTARI et al. (2017) developed nano-encapsulated chrysin-curcumin with PLGA-PEG copolymers, demonstrating anticancer activity in different models. JAVAN et al. (2019) demonstrated synergistic antiproliferative effects of co-nanoencapsulated curcumin and chrysin on MDA-MB-231 breast cancer cells.

VEDAGIRI & THANGARAHAN (2016) developed solid lipid nanoparticles of chrysin with stearic acid, lecithin and taurocholate. For this, stearic acid was maintained at ~75 °C to melt completely, simultaneously distilled water was heated up to ~75 °C in a separate beaker. Typically, surfactants were added to distilled water on a magnetic stirrer and allowed to equilibrate at ~75 °C. The water-surfactant solution containing chrysin was then added to the melted lipid and again allowed to equilibrate at ~75 °C. The mixture was then homogenized at 24,000rpm for 150s to form the emulsion. Then the aliquot was continuously stirred near ice cold water (~2 °C), at a ratio of 1:20 (warm microemulsion/cold water) resulting in the formation of solidified solid lipid nanoparticles. The final product was centrifuged at 20,000×*g* for 15min, and nanoparticle pellet was resuspended in distilled water. The preparation was stored in a sterile vial at 4 °C, until use. Similarly, PANDEY et al. (2021) and KOMATH et al. (2018) demonstrated in vitro anti-cancer activity of solid lipid nanoparticles of chrysin.

JASIM et al. (2022) showed gold nanoparticles conjugated chrysin. In this article, chrysin was dissolved in 5 mL of DMSO and stirred at 1,000 rpm for 15 min under room temperature to obtain a homogeneous solution with complete and clear visible solubility. The chrysin suspension was added to the solution of Au nanocapsules (1:9 mL) and stirred for 20 h, through overnight at room temperature. The color of the solution changed to light violet, and the excess chrysin was removed by ultracentrifugation. Furthermore, SATHISHKUMAR et al. (2015) report a new approach to formulate biofunctionalized metallic silver (chrysin-Ag), and gold (chrysin-Au) nanoparticles.

LUO et al. (2022) presented methoxy poly(ethylene glycol)-b-poly(e-caprolactone) (MPEG-PCL) nanomicelles platform for synergistic metformin and chrysin delivery to breast cancer in mice. For this, chrysin and metformin drug-loaded micelles were prepared by modified thin-film hydration. The specific operation was as follows: 50, 70, and 90 mg of polymer with different molecular weights were accurately weighed, mixed with chrysin and metformin, and placed in a rotary flask. About 2 mL of DCM was added and dissolved completely

by ultrasound. The organic solvent was removed by 0.07 MPa spin evaporation, and the bottle wall was covered with a film evenly distributed between drug and polymerdrug carrier material. Subsequently, 10 mL of re-distilled water was added to hydrate at 40 °C, 60 °C, and 80 °C and then cooled to room temperature after hydration. A 0.22 μm microporous filtration membrane was used to remove the uncoated chrysin and metformin and insoluble impurities. The solution of chrysin and metformin nano-micelles was obtained and stored in a refrigerator at 4 °C for future use. Similarly, KIM et al. (2017) showed improved chemotherapeutic efficacy of injectable chrysin encapsulated by MPEG-PCL nanoparticles.

ROY et al. (2020) developed chrysin loaded nanoparticle by the solvent displacement method. In this research, 100 mg of PLGA and 10 mg of chrysin were dissolved in 20 ml of acetone. This solution was poured dropwise overnight under magnetic stirring on an aqueous solution of 1% PVA. The solution was then centrifuged, and the precipitate was lyophilized.

MENON et al. (2018) evaluated the sustained release of chrysin from chitosan-based scaffolds. In this paper, scaffolds were prepared using simple ionic gelation method. Briefly, carboxymethyl cellulose (1% w/v) was dissolved in distilled water with continuous agitation. Chrysin, at different concentrations (2, 5, and 10 μM), in DMSO was added drop-wise. Chitosan (1% w/v) was added subsequently and stirred for 10 min, followed by addition of nano-hydroxyapatite (1% w/v). After 3 h of stirring, acetic acid (0.3% v/v) was added spontaneously, and the solution was cast into plates. The plates were maintained at −20 °C overnight, followed by lyophilization. The lyophilized scaffolds were crosslinked using 50 mM 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and maintained at 4 °C overnight, followed by lyophilization for 24 h. Similarly, SIDDHARDHA et al. (2020) showed that chrysin-Loaded chitosan nanoparticles potentiates antibiofilm activity against Staphylococcus aureus. FARHADI et al. (2023) presented anticancer effects of chrysin-loaded chitosan-folic acid coated solid lipid nanoparticles in pancreatic malignant cells.

Thus, there are so far a variety of methodologies used to encapsulate chrysin (summarized in Table 1), and it is up to scientists to choose the methodology to be used in their experiment, always seeking to optimize techniques, seeking to increase the bioavailability of the chrysin combined with the reduction of costs and time. We also found that there is a strong need the development of green methodologies for chrysin encapsulation, as most methods use highly toxic reagents such as DMSO, DCM and methanol. In this sense, some studies have have pointed to green alternatives, such as the use of lipid-water emulsions (VEDAGIRI & THANGARAHAN., 2016), dissolution of chrysin in ethanol (ZHU et al., 2016), and others. In addition, other techniques currently used can also be tested, such as spray drying, ionic gelation and coacervation.

Bioactive potencial of capsules

KHALID & NASEEM (2022) showed the antidiabetic and antiglycating potential of chrysin nanocapsules on *in vitro* studies. For this, antioxidant potential was determined and *in vitro* anti-diabetic activity was assessed by α-amylase and α-glycosidase inhibition assays and the results showed a dose-dependent increase in percent inhibition of the enzyme. Glycation was reduced to a high extent in presence of chrysin nanoparticles as compared to its bulk form and this was estimated by decrease in synthesis of Amadori products as well as advanced glycation end products. The results were further confirmed by spectroscopic techniques showing structural changes in human serum albumin glycated in the absence and presence of chrysin or its nanoparticle. The antiglycating effect was also evident by estimating free lysine residues, and protein oxidation.

EATEMADI et al. (2016) evaluated the effect of nano-chrysin on breast cancer cell line. Dataanalysis from MTT ((3(4, 5-dimethylthiazol-2-yl) 2, 5-diphenyl-tetrazolium bromide) assay showed that chrysin has a time-dependent cytotoxic effect on T47D cell line. Furthermore, the results of Real-time PCR suggested that encapsulated chrysin has higher antitumor effect on gene expression of FTO, BRCA1 and hTERT than free chrysin. Thus, combined nano-chrysin therapy will not only improve cancer cell cytotoxicity, but also be a complementary and potential complex in breast cancer therapy.

JABBARI et al. (2018) showed that viability of human lung epithelial cancer cell lines (A549) was significantly decreased upon interaction doxorubicin and chrysin-loaded (PLGA-co-PMAA) nano-formulation.

FIROUZI-AMANDI et al. (2018) investigated the efficiency of chrysin encapsulated in PLGA-PEG nanoparticles for the modulation of macrophage polarity from the pro-inflammatory M1 to anti-inflammatory M2 phenotype. Findings revealed that the chrysin-encapsulated were considerably less toxic to the macrophages. Additionally, the nano-

Table 1 - Summary of encapsulation methods and bioactive potential of capsules containing chrysin. The works are organized in chronological order.

Summarized Methodology	Biological Potential	Reference
Dissolution in PCL-PEG-PCL in DCM + dH_2O + Sonication + Solvent evaporation	Anticancer in breast cancer cell line	EATEMADI et al. (2016)
Mix of water-surfactant solution containing chrysin and stearic acid completely melted + Equilibrate at ~75 °C + Homogenization + Agitation near ice cold water + Centrifugation + Resuspension of pellet in distilled water	Ameliorates neurobehavioral alterations of Alzheimer's	VEDAGIRI & THANGARAHAN (2016)
Dissolution of chrysin in ethanol + Recrystallizated β-cyclodextrin dissolved in H_2O with continuous stirring + Crystallization in refrigerator + Vacuum filtration + Drying	Antioxidant, antimicrobial and anti-tumor activity	ZHU et al. (2016)
Dissolution with PLGA-PEG tri-block copolymer in DCM-methanol + Agitation + PVA + sonication + Vacuum vaporization of the solvent + Centrifugation + Washing with dH_2O + Lyophilization	Possible aplicattion in tissue regeneration	FIROUZI-AMANDI et al. (2018)
Addition in dozorubicin/(PLGA-co-PMAA) copolymer + Sonication + PVA and agitation + Centrifugation + Washing with dH_2O and centrifugation	Anticancer effect in lung epithelial cancer cell lines	JABBARI et al. (2018)
Dissolution of carboxymethyl cellulose in dH_2O + Addition of chrysin dissolved in DMSO + Addition of Chitosan + Agitation + Addition of nano-hydroxyapatite + Agitation + Addition of acetic acid + Solution cast into plate + Lyophilization	Mesenchymal stem cell proliferation and osteoblast differentiation	MENON et al. (2018)
Dissolution of chrysin in DMSO + Addition of chrysin solution to BSAnp in PBS + Agitation	Antitumor therapies	FERRADO et al. (2019)
Dissolution with poly(ε-caprolactone), pomegranate oil, and sorbitan monostearate in acetone + Addition to the aqueous phase (polysorbate H_2O) with magnetic stirring + Acetone evaporation by rotary evaporator + Concentration of suspensions under reduced pressure	Ameliorates neurobehavioral alterations of Alzheimer's disease in mice	GIACOMELI et al. (2020)
Dissolution of chrysin and curcumine in PLGA/PEG + Magnetic stirring + Electrospinning + Nfs drying in a vacuum oven	Effect on T47D breast cancer cells	RASOULI et al. (2020)
Dissolution of chrysin and PLGA in acetone + Mix with PVA + Centrifugation + Lyophilization	Attenuation of allergic asthma	ROY et al. (2020)
Dissolution with PLGA, Labrafac PG and phosphatidylcholine in acetone + Addition dropwise to an aqueous solution of tween 80 placed on a magnetic stirrer + Evaporation of the organic solvent	Anti-glycemic and anti-hyperlipidemic	EL-HUSSIEN et al. (2021)
Dissolution of chrysin in DMSO + Agitation + Addition to Au nanocapsules solution + Agitation + Centrifugation	Antioxidant, anti-microbial and cytotoxic	JASIM et al. (2022)
Dissolution in DCM and acetone + Emulsification with PVA + Centrifugation + Supernadant discard + Drying and pelletizing	Antioxidant, antidiabetic and antiglycating	KHALID & NASEEM (2022)
Chrysin and metformin mixed with polymer + Placed in rotary flask + Addition of DCM + Sonication + Solvent evaporation + Hydration + Filtration	Effect in breast cancer in mice	LUO et al. (2022)

formulated chrysin efficiently showed a reduction in M1 markers and an increase in M2 markers levels than free chrysin. Furthermore, macrophage phenotype switching by PLGA-PEG encapsulated chrysin significantly suppressed LPS/IFN-γ induced inflammation by a remarkable reduction in pro-inflammatory cytokine levels, TNF-α, IL-1β, and IL-6. Results revealed that PLGA-PEG encapsulated chrysin based drug delivery system might be introduced into biomaterials to fabricate bioactive smart multifunctional nanocomposites with macrophage repolarization activities for regenerative medicine purposes.

EL-HUSSIEN et al. (2021) showed anti-glycemic and anti-hyperlipidemic effects of chrysin nanocapsules in rats. Diabetes was induced in an animal model using strptozotocin to assess the anti-hyperglycemic activity, and hyperlipidemia was induced using a high fat diet to assess its anti-hyperlipidemic activity.

GIACOMELI et al. (2020) studied chrysin loaded lipid-core nanocapsules effect in neurobehavioral alterations induced by β-amyloid$_{1-42}$ in aged female mice. Results support that chrysin displayed significant effect against Aβ_{1-42}, via attenuation of oxidative stress and neuroinflammation, modulation of neurochemical and behavioral changes in a model of Alzheimer's disease.

FERRADO et al. (2019) did not perform bioactive potential assessments, but suggested that their results highlighted the ability of self-assembled BSAnp for chrysin vehiculization in an aqueous

medium, which could found potential application in antitumor therapies.

ZHU et al. (2016) presented inclusion of chrysin in β-cyclodextrin and its biological activities. The process of inclusion not only increased the solubility of chrysin but also its antioxidant potential, antimicrobial activity and anti-tumor activity on mouse hepatoma H22 cells.

RASOULI et al. (2020) showed that co-delivery of curcumin and chrysin through a polymeric electrospun nanofibrous scaffold exerts a synergistic anti-proliferative and pro-apoptotic effect on T47D breast cancer cells. In this study, dual drug-loaded nanofibrous showed an excellent capacity to inhibit T47D breast cancer cells *in vitro* than the single drug-encapsulated nanofibrous. Therefore, the fabricated dual drug-encapsulated nanofibrous may achieve a safe and suitable application for breast cancer relapse rate after surgery.

VEDAGIRI & THANGARAHAN (2016) demonstrated effect of chrysin loaded solid lipid nanoparticles against Amyloid β_{25-35} induced oxidative stress in rat hippocampal region. In this paper, all the antioxidant enzymes and non-antioxidant enzyme in hippocampus were reduced in the Aβ25–35 injected group, whereas lipid peroxidation and acetylcholine were increased. In addition, Aβ25–35 also resulted in poor memory retention in behavioral tasks and histopathological sections of the hippocampal region showed the extent of neuronal loss. These changes were restored significantly by chrysin nanoparticles.

JASIM et al. (2022) presented an assessment of antioxidant, anti-microbial, and in vitro cytotoxic activities of the gold nanoparticles conjugated chrysin. The chrysin-Au nanocapsules effectively scavenged the 2,2- diphenyl-1-picrylhydrazyl free radicals, and exhibited potential cytotoxic effects in a dose-dependent manner and demonstrated significant reduction of the cells proliferation, and growth of the human breast cancer celllines, AMJ13. Furthermore, chrysin-Au nanocapsules exerted highest anti-microbial bioactivity against.

Staphylococcus aureus and *Escherichia coli*.

LUO et al. (2022) showed MPEG-PCL nanomicelles platform for synergistic metformin and chrysin delivery to breast cancer in mice. In this paper, metformin/chrysin co-delivery micelles showed a good synergistic effect on inhibiting proliferation in T47D cells by suppressing hTERT and cyclin D1 gene expression. The tumour volume and tumour weight of the metformin/chrysin group increased more slowly than that of the single-drug treatment group.

ROY et al. (2020) demonstrated that chrysin-loaded PLGA attenuates ovoalbumin-induced allergic asthma by modulating TLR/NF-κB/NLRP3 axis. In this research, the spherical nanosized particles showed slow, sustained release in vitro. Moreover, nanocapsules dramatically reduced the serum IgE, ovoalbumin-induced lung histological alteration, as well as Th2 (T-helper 2) cytokines in the bronchoalveolar lavage fluid. It also suppressed the elevated serum pro-inflammatory cytokines and their upstream TLR/NF-κB/NLRP3 pathway activation in lung superior to chrysin and almost identical to dexamethasone.

MENON et al. (2018) showed that sustained release of chrysin from chitosan-based scaffolds promotes mesenchymal stem cell proliferation and osteoblast differentiation. In this article, chrysin-containing scaffolds were not cytotoxic to mouse mesenchymal stem cells. Chrysin released from scaffolds stimulated cell proliferation and promoted osteoblast differentiation. Osteoblast differentiation enhanced by chrysin from scaffolds could be due to downregulation of co-repressors of the osteoblast differentiation transcription factor Runx2 in these cells.

In view of afore mentioned, the main biological potential of capsules containing chrysin, in order to facilitate visualization by readers, are depicted in table 1.

In addition, other authors have also developed and evaluated biologic potential of capsules containing chrysin. NOSRATI et al. (2018) studied activity of L-phenyl alanine-coated iron oxide magnetic nanoparticles as potential chrysin delivery system. WANG et al. (2015) developed chrysin-nanosuspension composed of chrysin and poloxamer 188 prepared by high pressure homogenization technique. The *in vitro* anti-hepatocarcinoma effect was showed. KAMAT et al. (2022) demonstrated apoptotic effect of nano-chrysin (using PLGA polymer) in HeLa cells. TING et al. (2021) developed chrysin-loaded oil-in-water nanoemulsions and demonstrated in vitro antioxidant and anti- Alzheimer's disease. KHOSHRAVAN et al. (2022) showed the development of nanostructured co delivery of artemisinin and chrysin for targeting hTERT gene expression in breast cancer cell line. HALEVAS et al. (2021) presented the evaluation of the hemocompatibility and anticancer potential of poly (ε-Caprolactone) and poly(3-Hydroxybutyrate) microcarriers with encapsulated chrysin. BAIDYA et al. (2019) showed chrysin-loaded folate conjugated PF127-F68 mixed micelles with enhanced oral bioavailability and anticancer activity against human breast cancer cells.

TARAHOMI et al. (2023) demonstrated niosomes nanoparticles as a novel approach in drug delivery enhances anticancer properties of chrysin in human ovarian carcinoma cells (SKOV3). ABDELHAKM et al. (2023) presented that chrysin encapsulated copper nanoparticles with low dose of gamma radiation elicit tumor cell death through p38 MAPK/NF-κB pathways. DESHMUKH et al. (2021) showed chrysin liposomes for breast cancer treatment. Chrysin liposomes were developed by electrostatic deposition assisted film hydration method using chitosan/ lecithin to protect chrysin in the nano-lipoidal shell. Some other works also presented the bioactive effects of lipossomal chrysin, as HUANG et al. (2022) and BEYRAMI et al. (2020).

CONCLUSION

In conclusion, we observed that encapsulation methods of chrysin are diverse, and the most recurrent encapsulating agents were PEG, PLGA polymers and their derivatives, in addition to other agents, such as PCL, albumin, lipids and chitosan.

We believed that the information presented in this article will point the way for researchers in choosing flavonoid encapsulation methodologies, considering their possibilities and working conditions, always seeking to optimize techniques, seeking to increase the bioavailability of the chrysin combined with the reduction of costs and time. We also found that there is a strong need the development of green methodologies for chrysin encapsulation, as most methods use highly toxic reagents such as DMSO, DCM and methanol. In this sense, some studies have have pointed to green alternatives, such as the use of lipid-water emulsions and dissolution of chrysin in ethanol. In addition, other techniques currently used can also be tested, such as spray drying, ionic gelation and coacervation.

The bioactive effects of the capsules are also numerous, and anticarcinogenic effects are the most frequent, in addition to other effects, such as antioxidant, antidiabetic, antimicrobial and neuroprotective. Furthermore, bioactive potential of these capsules can be evaluated in other experimental models, and should advance to clinical trials and application in food formulations.

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DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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