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NANOTECHNOLOGY ASSOCIATED WITH GRAPE SEED EXTRACT AND APPLICATIONS[1]

NANOTECNOLOGIA ASSOCIADA A EXTRATO DE SEMENTE DE UVA E SUAS APLICAÇÕES

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ABSTRACT

The aim of this study was to investigate the main nanostructures used to protect polyphenols present in grape seed extract and their actions. This study is an integrative review of the literature. The data collection was performed on 31st may, 2019, in the electronic databases Web of Science and Bireme (Virtual Health Library). The Boolean descriptors and operators used were: Nano* AND Grape seed AND Extract. English, Spanish or Portuguese were included in the sample. The search in the databases resulted in the collection of 132 articles, of which 12 fulfilled the inclusion criteria. As all the nanoparticles containing grape seed extract maintained or increased the activity of the polyphenols present in the extract, thus showing that the use of nanotechnology is effective in protecting these bioactive compounds and can be used in health and food industry.

Keywords: antioxidant, nanoparticle, oxidative stress, polyphenols.

RESUMO

O objetivo deste estudo foi investigar as principais nanoestruturas utilizadas para proteger polifenóis presentes no extrato de semente de uva e suas ações. Este estudo é uma revisão integrativa da literatura. A coleta dos dados foi realizada no dia 31 de maio de 2019, nas bases de dados eletrônicos Web of Science e Bireme (Biblioteca Virtual em Saúde). Os descritores e operadores boleanos utilizados foram: Nano AND Grape seed AND Extract. Foram incluídos na amostra artigos nos idiomas inglês, espanhol e português. A busca nas bases de dados resultou na coleta de 132 artigos, dos quais 12 preencheram os critérios de inclusão. Sendo que todos os nanopartículas contendo extrato de semente de uva mantiveram ou aumentaram a atividade dos polifenóis presentes no extrato, mostrando assim que o uso da nanotecnologia é eficaz na proteção destes compostos bioativos, podendo ser utilizados na saúde e na indústria alimentícia.*

Palavras-chave*: antioxidante, estresse oxidativo, nanopartícula, polifenóis.*

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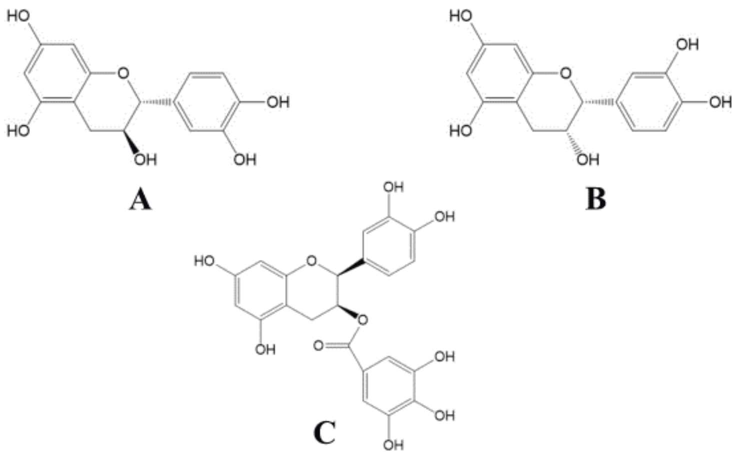
INTRODUCTION

Grape Seed Extract (GSE) is a blend of polyphenols, where essentially all flavonoids, which have a class called flavan-3-ol, are divided into monomers, dimers and trimers. Catechin, epicatechin and epicatechin-3-O-gallate (Figure 1) are reported monomers in GSE (NACZK; SHAHIDI, 1991). Flavan-3-ols readily condenses on oligomeric procyanidins and polymeric compounds (condensed tannins). The dimeric procyanidins are often referred to as the B series and the trimeric procyanidins as the C series. Five different dimers (procyanidin B1, B2, B3, B4 and B5) (Figure 2) and two trimers (C1 and C2) (Figure 2) were identified from grape rind and seeds. These dimers and trimers are composed of catechins and epicatechins (SHI et al., 2003). In summary, the main phenolic compounds present in the GSE are shown in Figure 3.

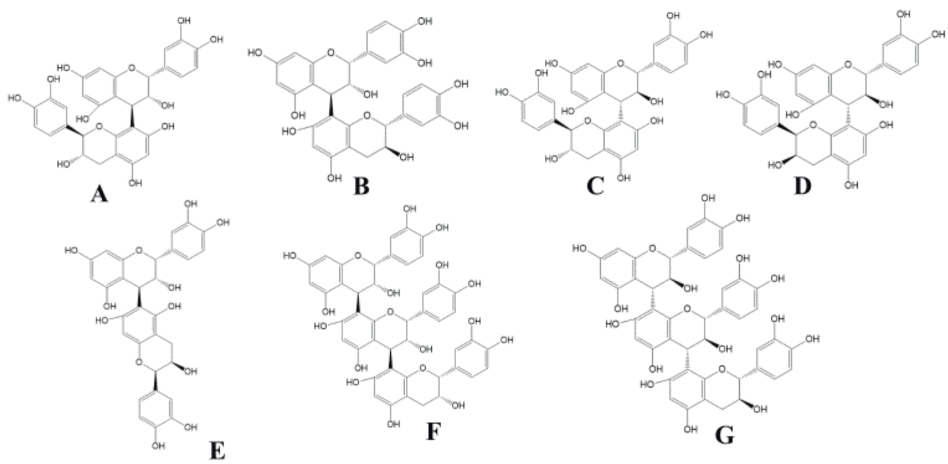
Figure 1 - Chemical Structure of Flavan-3-ols Monomers.



Catechin (A) Epicatechin (B) Epicatechin-3-O-Gallate (C)

Source: Elaborated by the authors by ChemDraw Professional 16.0 Software.

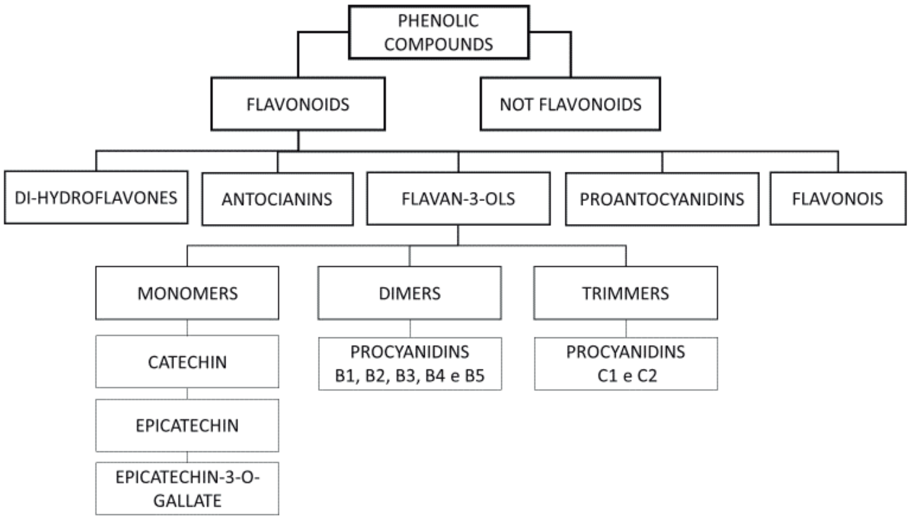
Figure 2 - Chemical structure of dimeric and trimeric procyanidins.



Procyanidin B1 (A) Procyanidin B2 (B) Procyanidin B3 (C) Procyanidin B4 (D) Procyanidin B5 (E) Procyanidin C1 (F) Procyanidin C2 (G)

Source: Elaborated by the authors by ChemDraw Professional 16.0 Software

Figure 3 - Flowchart of the main phenolic compounds present in Grape Seed Extract.



Source: Elaborated by the authors.

The promotion of health and disease prevention of phenolic compounds are due to their beneficial physiological properties, including antioxidants, anti-inflammatory, anticancer, antimicrobial and anti-aging (XIA et al., 2010). These properties of polyphenols are mainly due to the elimination of reactive oxygen and nitrogen species, and the increase in the endogenous antioxidant capacity of the cells/tissues, and glutathione synthesis or influence the signaling pathways through the interaction with cellular receptors and enzymes (VALKO et al., 2006).

However, the main obstacles of dietary polyphenols include their low solubility and high chemical instability that result in low bioavailability, low permeability and degradation before reaching the systemic circulation (GIBIS; RUEDT; WEISS, 2016). In order to improve the stability and bioavailability of the polyphenols, nanoencapsulation techniques are used, thus the shelf-life of the encapsulated substances can be extended and release may be controlled (AIZPURUA-OLAIZOLA et al., 2016).

Due to the importance of polyphenols in grape seed extract, the purpose of this literature review was to investigate the main nanostructures used to protect these polyphenols and their applications.

MATERIAL AND METHODS

This study is characterized as exploratory, type integrative literature review. The search for the studies took place on 31st may, 2019, in the electronic databases Web of Science and Bireme (Virtual Health Library). The Boolean descriptors and operators used were: Nano * AND Grape seed AND Extract.

The inclusion criteria used to select the articles were: complete articles and available online in full, published in the Portuguese, English or Spanish languages, which used nanostructures to protect the polyphenols contained in the grape seed extract. Bibliographic review studies and articles in duplicate were excluded from the sample.

After searching the databases, the titles and abstracts were evaluated and the studies that included the inclusion criteria were selected for reading in their entirety. The following characteristics of the publications were recorded in Table 1: reference, nanoparticle and main destination of nano-encapsulated grape seed extract.

Table 1 - Summary of publications that comprised the study sample, emphasizing the study group, nanoparticle type, and main fate in Nanoencapsulated Grape Seed Extract, published from 2010 to 2019, based on data provided by the Web of Science and Bireme.

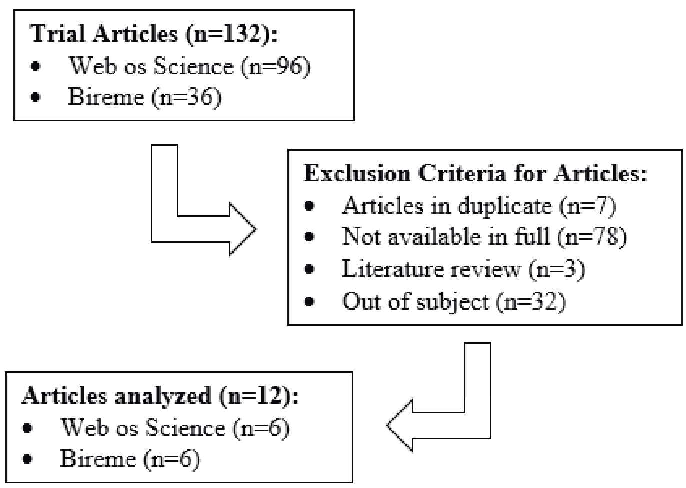
Reference	Nanoparticle Type	Main Destination
Locilento et al. (2019)	Nanofibrous membranes	Antioxidant Dressings
Ranoszek-Soliwoda et al. (2019)	Silver nanoparticle	Synthesis Protocol
Castellani et al. (2018)	Solid lipid nanoparticle	Oxidative stress
Sogut; Seydim (2018)	Nanocellulose film	Food Packaging
Fernández et al. (2017)	Nanoparticle of polylactic acid	Increased intestinal absorption
Kumawat et al. (2017)	Graphene Quantum Dots	Cell viabilily in fibroblastos
Loureiro et al. (2017)	Solid lipid nanoparticle	Treatment of Alzheimer's disease
Abdelaleem et al. (2016)	Selenium Nanoparticle	Treatment of diabetes
Lin et al. (2016)	Nanofibers	Tissue regeneration
Preethi e Padma (2016)	Silver nanobioconjugate	Antimicrobial
Felice et al. (2013)	Polymer Nanoparticles	Protection of endothelial progenitor cells
Narayanan et al. (2010)	Nanoparticles of poly (lactic-co-glycolic acid)	Chemotherapeutic

Source: Elaborated by the authors from the results obtained in the Web of Science and Bireme databases.

RESULTS AND DISCUSSION

The search in the databases resulted in the collection of 132 articles, of which 12 adequately met the criteria and were selected for inclusion in the study. Figure 4 shows the flowchart with the selection strategy of the included articles. The publications that composed the study sample were published between the years 2010 and 2019.

Figure 4 - Flowchart with the article selection strategy.



Source: Elaborated by the authors from the results obtained in the Web of Science and Bireme databases.

This study showed that nanoparticles used to protect GSE were polymeric nanoparticles such as PLGA and PLA, mineral nanoparticles such as selenium and silver, graphene quantum dots, solid lipid nanoparticles, nanofibers and cellulose films. The main applications of these GSE-containing nanoparticles were for chemotherapeutic use, progenitor cell protection, diabetes and Alzheimer's disease treatment, tissue regeneration, antimicrobial, fibroblast cell viability, oxidative stress, food packaging and antioxidant dressings (Table 1).

Locilento et al. (2019) developed biocompatible and biodegradable nanofibrous membranes with antioxidant properties, using polylactic acid (PLA) and polyethylene oxide (PEO) as matrix, with the addition of grape seed extract (GSE), a rich source of natural antioxidants. The results of Fourier Transform Infrared and Thermogravimetry showed that the GSE was efficiently encapsulated in the membranes, whose antioxidant activity was preserved. The GSE release profile of the polymer membranes was dependent on the composition of the nanofiber, where the addition of a hydrophilic polymer extended the period of GSE release. Therefore, developed nanofibrous membranes may be a viable alternative to a new generation of antioxidant dressings.

Lin et al. (2016) manufactured a nanofibrous blanket composed of silk fibroin (SF) / polyethylene oxide (PEO) loaded with grape seed extract (GSE) by electrowinning. The results indicated that the loading was successful, the introduction of GSE did not affect the morphology of the nanofibres, besides being released in a sustained way. In addition, the GSE-loaded mantle significantly increased the proliferation of skin fibroblasts and protected them against damage caused by oxidative stress induced by tert-butyl hydroperoxide. All of these findings suggest a promising potential of this nanofiber composed of SF / PEO loaded with GSE applied in skin care, tissue regeneration and wound healing.

Locilento et al. (2019) and Lin et al. (2016) developed nanofibers with GSE, which due to the antioxidant activity of the extract achieved tissue regeneration, thus being able to use GSE in dressings, wound healing and other skin care. Abdelaleem et al. (2016) and Preethi; Padma (2016) used minerals such as selenium and silver to carry the polyphenols contained in GSE. The extract, associated with minerals, was used in the treatment of diabetes and also obtained an antimicrobial activity, being a potential in the use of biomedicine. In contribution, Ranoszek-Soliwoda and colleagues (2019) published a protocol for obtaining monodisperse silver nanoparticles from plant extracts, such as GSE.

In the work developed by Abdelaleem et al. (2016) evaluated the protective role of the mixture of grape seed extract and selenium nanoparticles (SeNPs-GSE) in improving the changes in the gamma radiation-induced oxidative stress biomarkers in diabetic rats. Forty-eight rats were randomly assigned to 6 experimental groups: normal, diabetic, irradiated, irradiated diabetic, diabetic treated with SeNPs-GSE or glimepiride (1 mg) for fourteen consecutive days of radiation. Where results in the study indicated that diabetic rats treated with SeNPs-GSE or glimepiride prior to radiation exerted a significant improvement in all biochemical parameters tested, thus showing that NP possesses antioxidant and antidiabetic activity, decreasing stress biomarkers oxidative stress, as well as blood glucose level, thus exhibiting activity similar to glimepiride.

The study published by Preethi; Padma (2016) deals with the synthesis of silver nanobio-conjugates from the methanolic extract of grape seeds and the pure compound resveratrol. Several conditions were applied to influence the rapid reduction of Ag+ to Ag, such as microwave heating, water bath heating, exposure to sunlight and incubation at 37 ºC for the synthesis of nanobioconjugates. Among the four different methods, exposure to sunlight proved to be rapid in synthesis and the yield of nanobioconjugates was also high. Therefore, this method was chosen for the synthesis of silver nanobioconjugates using resveratrol. The bioactivity of the synthesized silver nanoconjugates was also evaluated through antimicrobial activity. Additionally, it was observed that the extract and compound nanobioconjugates were more effective than their unconjugated equivalents, indicating potential biomedical applications.

The study carried out by Ranoszek-Soliwoda et al. (2019) brought a synthesis protocol for obtaining monodisperse silver nanoparticles (AgNPs) with vegetal extract. Cocoa bean and grape seed extracts were selected as natural sources of polyphenols of biomedical importance (eg catechin, tannic acid, epicatechin gallate) using a chemical reduction method. The obtained colloids were characterized by ultraviolet-visible (UV-Vis) spectroscopy, scanning electron microscopy and dynamic scattering of light. It was found that syntheses carried out with plant extract only resulted in unstable colloids containing polydisperse nanoparticles. Stable colloids containing spherical monomodal particles were obtained by incorporating sodium citrate as additional reagent into the synthesis mixture.

In the study of Castellani et al. (2018) a drug release system based on solid lipid nanoparticles (SLN), capable of encapsulating the grape seed extract (GSE) containing proanthocyanidins was developed. SLN were not cytotoxic when incubated with H441 airway epithelial cells as judged by both the propidium iodide (PI) and spectrophotometry (MTT) assays, as well as by apoptosis/necrosis evaluation. The SLN-GSE obtained 243 nm as medium diameter, negatively charged and stable at 37 °C in Simulated Pulmonary Fluid up to 48h, and in bidistilled water at 4 °C for up to 2 months. The SLN loaded with GSE determined a significant reduction in the production of reactive oxygen species (ROS) when added 24-72 h prior to stimulation with hydrogen peroxide.

The study by Loureiro et al. (2017) showed that solid lipid nanoparticles (NLSs) functionalized with anti-transferrin receptor monoclonal antibody (OX26-mAb) can function as a possible vehicle for transporting the grape seed extract and peel of grape, to reach the brain and be used in the treatment of Alzheimer's disease (AD). Extracts strongly inhibit the formation of Aβ (1-42) fibrils and have a more pronounced inhibitory effect compared to pure resveratrol, thus showing that extracts in addition to resveratrol inhibit Aβ (1-42) aggregation, and have other polyphenols that make this inhibitory effect more pronounced. The SLNs remained stable for at least 1 month and their uptake by blood-brain barrier cells was increased with antibody functionalization.

Castellani et al. (2018) and Loureiro et al. (2017) chose to nanoencapsulate the GSE through solid lipid nanoparticles, with the purpose of reducing oxidative stress and treating Alzheimer's Diseases, respectively. Fernández and collaborators (2017); Felice et al. (2013) and Narayanan et al. (2010) used polymeric nanoparticles to protect the polyphenols contained in the GSE, thereby increasing the intestinal absorption of these compounds and also being used to protect endothelial progenitor cells from oxidative stress and use as chemotherapy.

In the research by Fernández et al. (2017), the intestinal absorption of seed and grape skin extracts and the polylactic acid nanoparticles (PLA) loaded with such extracts was modeled. The physical-chemical process parameters, density (ρ), solubility, viscosity (μ), diffusion coefficient (D) and overall mass transfer coefficient (K) for both substrates were estimated by simulating their passage from the intestine to the blood at 37 ° C. In particular, for seed extracts and pellets nanoencapsulated in PLA, K increased 33 and 48 times, and D was 10 and 23 times higher than for crude extracts, respectively. Thus, the encapsulation of the extracts was favorable, which should reduce the resistance to mass transfer. The concentration of grape skin and seed extracts in the small intestine was modeled using a pure convection model and the encapsulated PLA nanoparticle extract using a mixed regime model, which described the process of dissolution and absorption of grape extract small intestine bloodstream. The extracted encapsulation increased the absorbed fraction to 100% compared to the crude extracts, where complete absorption was not achieved for any of the extracts. Thus, encapsulation of the extract should produce a significant increase in intestinal absorption.

In the study by Felice et al. (2013), they evaluated the validity of mucoadhesive polymeric nanoparticles (NP), loaded with pre-ripening (p-GSE) and mature (m-GSE) seeds, in order to protect endothelial progenitor cells (EPCs) from oxidative stress. Both types of GSE demonstrated strong antioxidant capacity. The p-GSE presented higher content in total polyphenols compared to m-GSE. The NP sizes were in the range of 310 - 340 nm, with 24 hours stability and almost 100% encapsulation efficiency for both GSE types. Uptake of GSE-NP significantly improved cell viability and oxidation resistance.

Narayanan et al. (2010) produced nanoparticles of poly (lactic acid-co-glycolic acid) (PLGA) nanoencapsulating the grape seed extract (GSE), which was prepared by a nanoprecipitation technique. Nanoparticles of average size of 100 nm exhibited high colloidal stability at physiological pH. Successful bioconjugation of NanoGSE with folic acid as the targeting ligand provided increased cell uptake as well as inhibition of cell growth due to the targeted and controlled delivery of the nutraceutical. The targeting effect was investigated by incorporating folate-conjugated rhodamine-123-loaded NanoGSE cancer cells using fluorescence microscopy. Thus, providing convincing evidence of drug delivery based on nanotechnology to increase the therapeutic efficacy of this known green chemotherapeutic agent.

In the work published by Sogut; Seydim (2018), nanocellulose (NC) and grape seed extract (GSE) films, added with chitosan (CH) and polycaprolactone (PCL) were prepared by or coating with PCL in the form of chloroform solution (C-PCL) or compression of PCL and CH (P-PCL) layers.

The incorporation of NC significantly reduced the permeability to the water value (WVP) and the opacity of the films, while the addition of GSE had an adverse effect. The P-PCL films presented higher modulus of elasticity, tensile strength and WVP values and lower elasticity when compared to C-PCL films. All film samples showed antimicrobial activity and GSE retained its antioxidant capacity within the CH matrix. The formation of two-layer films based on CH and PCL with NC and GSE improved the suitability of CH films for food packaging applications.

GSE's antioxidant activity goes beyond its use in human health, as shown by Sogut; Seydim (2018), which produced nanocellulose and extract films for the purpose of protecting food through packaging. Finally, Kumawat et al. (2017) synthesized Graphene Quantum Dots using extract to increase cell viability in fibroblasts.

Kumawat et al. (2017) reported a green synthesis assisted microwave graphon of Quantum Dots using grape seed extract as a source of green therapeutic carbon. The self-assembled Quantum Dots Graphene (sGQDs) enter via cavity-mediated endocytosis and clathrin, and go to the cell nucleus in 6-8h. The tendency to self-localize in the cell nucleus also remains consistent in different cell lines such as L929, HT-1080, MIA PaCa-2, HeLa and MG-63 cells, thus serving as a core labeling agent. In addition, sGQDs are highly biocompatible and act as a potentiator in cell viability in mouse fibroblasts as confirmed by the in vitro scratch test and cell cycle analysis. In addition, the photoluminescence property of sGQDs was used for the application of the optical pH sensor. The sGQDs show a linear, cyclical and reversible trend in their fluorescence intensity between pH 3 and pH 10, thus serving as a good pH sensing agent. A sGOD based on a simple, economical, scalable, and green synthetic approach can be used to develop selective organelle labeling, nucleus targeting in terostatic tests and optical sensing probes.

CONCLUSION

The present study showed that grape seed extract can be protected by different types of nanoparticles, such as polymeric nanoparticles, mineral nanoparticles, graphene quantum dots, solid lipid nanoparticles, nanofibers and cellulose films. Thus, maintaining or increasing the action of the polyphenols contained in the extract and can be used for several applications, such as chemotherapy, progenitor cell protection, diabetes and Alzheimer's disease treatment, tissue regeneration, antimicrobial, fibroblast cell proliferation, oxidative stress, food packaging and antioxidant dressings.

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