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ROLE OF NATURAL COMPOUNDS - ENCAPSULATED NANOPARTICLES IN DISEASES TREATMENT

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ABSTRACT: During the last decades, nanotechnology has entered in many areas and leads to amazing scientific developments Worldwide. Meanwhile, the pharmaceutical industry has not been deprived and nanotechnology inventions lead to supply new and innovative pharmaceutical products.In this study, we reviewed the role of nanoparticles with bioactive compounds in order to diseases treatment. In order to reach this purpose, we searched keywords such as nanoparticles and compounds and diseases, nanoparticles and drug delivery and diseases in databases including web of science, PubMed and Scopus. In the last decade, it has been confirmed use of nanotechnology-based drugs in order to increase their efficiency and effectiveness especially in pharmaceutical researches and clinical studies. Today, there are many systems based on nanoparticles for targeting and transport of drug. In fact, nanoparticles lead to reduction of drug destruction, inhibition of side effects and increase of bioavailability. In this paper, we reviewed effects of nanoparticles as carrying of compounds with bioactive property in the treatment of diseases.

INTRODUCTION: In recent years, to focus new drug delivery systems such as nano-drug in order to treatment of diseases significantly increases. In order to deliver of effective dose of drug and inhibition of side effects, pharmaceutical field require carriers with appropriate formulations. In this regard, the use of colloidal carriers such as liposomes and nanoparticles can be good strategies to achieve this goal. It has been demonstrated that delivery systems based on nanoparticles have good efficacy, less toxicity, more convenience for patient, as well as obvious bioavailability [1 - 3].

Generally, nano-particles have widespread use such as carrier for anti-microbial and anti-cancer drug as well as peptides and proteins such as insulin. In addition, the first nanoparticles have developed in order to production of vaccine against tetanus and diphtheria by Markle and Speiser [4].

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The nanoparticles are classified into two main groups including: the nanoparticles with organic molecules as the main material and another, nanoparticles with metals and minerals as main material [5 - 7]. There are several methods for nanoparticles preparing so that they provide major changes in the structure, composition and physico-chemical property. Selection of a method for nanoparticles producing is depended on drug solubility and its biological activity as well as particle size range. In the selection of raw materials needed to produce nanoparticles, features such as biocompatibility, degradation, administration method of final formulation and of the drug releasing should be considered [8]. In fact, by preparation of drug nanoparticles, can be achieved unique features that lead to a better efficacy and variety in drug forms.

In addition, their precise formulations of these particles lead to their more stability and can increase their dissolution and ultimately reach to their biological level. These events accelerate bioavailability and therapeutic effect of drugs. It has been showed that development of new drugs is not alone effective in drug therapy because low solubility of some drugs in water is considered as their main problem. Therefore, it seems that is very necessary to develop drug delivery systems for overcome these problems. These systems should be non-toxic carriers with high capacity for drug carrying and ability of drug releasing control [9].

Many drugs with various applications have successfully embedded in nanoparticles. These drug delivery systems lead to controlled releasing of drugs and increase their chemical stability. In addition, these systems are safe carriers that can be easily produced on a large scale [10 - 12]. The aim of this study was to review the effect of nanoparticles with bioactive compounds in treatment of diseases.

Review Method: In this study, we reviewed the role of nanoparticles with bioactive compounds in order to diseases treatment. In order to reach this purpose, we searched keywords such as nanoparticles and compounds and diseases, nanoparticles and drug delivery and diseases in databases including web of science, PubMed and Scopus. After searching, the paper were read and summarized here.

Role of Natural Compounds - Encapsulated Nanoparticles in Diseases Treatment: Ellagic acid is an antioxidant phenolic compound comprised four rings with hydroxyl groups and two lactone rings that reflect its hydrophilic part. Ellagic acid is dimer form of gallic acid and pomegranates, grapes and strawberries are rich of ellagic acid [13]. It has been reported range of activities such as antioxidant, antiviral and anticancer from this compound [14 - 16]. Ellagic acid is a commercial valuable compound that is used as capsule and powder for various diseases such as cancer and heart disease as a dietary supplement [15, 17]. It have been confirmed its anticancer property against in colon, liver and lung [18]. However, its low stability in aqueous solution and limited bioavailability has limited its use in the treatment [19]. This problem is solvable by nanotechnology and advances in the field of drug delivery for example; chitosan has necessary performance for this work.

In addition, liposomes, polymeric nanoparticles, lipid nanoparticles, cyclodextrin and hydrogel are appropriate candidates to achieve this idea [20]. Nevertheless, biopolymeric nanoparticles are widely used because it can prevent the destruction of the drug under *in vivo* condition and have great ability to transfer large amounts of the drug and can to the target location [21]. In addition, chitosan nanoparticle is used as a promising carrier for anticancer drugs [22]. Kim *et al*., in 2009 reported that chitosan can be a suitable carrier for transferring of ellagic acid to the tumor site because treatment of human melanoma cell lines (WM115) with chitosan nanoparticles carrying ellagic acid leads to reduction of cell growth of tumor and apoptosis induction [23].

Chitosan enhances antitumor activity of ellagic acid so that the nanoparticles of chitosan containing of ellagic acid results in reduction of growth, activation of caspase-3 in human U87 glioblastoma cell lines and rat C6 glioma at the end of treatment period. In addition, it could abrogate amount of tumor cells in rats with C6 glioma [24]. Arulmozhi *et al*., in 2013 indicated that ellagic acid encapsulated chitosan has many performances to destroy the human oral cancer cell line (KB) so that it reduced cancer cells significantly and induced apoptosis [25]. Nano-sized metalla-cages containing of ellagic acid has anti-cancer activity while free ellagic acid has

not obvious cytotoxic effect against granulocyte colony of T cell expression stimulating but nano-sized metalla-cages containing of ellagic acid reduced T cells expression in the macrophage cell line RAW264 [26].

In addition, alginate-silver nanoparticles increase efficiency of ellagic acid in treatment of breast cancer. In fact, treatment of MCF-7 as a breast cancer cell line by the ellagic acid encapsulated alginate-silver nanoparticles led to reduction of cancer cells [27]. Berberine is an isoquinoline alkaloid with therapeutic effects and found in plants such as *Coptis chinensis*, *Berberis aquifolium Berberis vulgaris* [28, 29]. It has been demonstrated wide range of biochemical and pharmacological activities such as antidiarrheal and anti-cancer effects from berberine [30, 31]. Today, the uses of nanoparticles have increased to transfer compounds with therapeutic features [32]. In a study, it was showed that berberine conjugated with silica nanoparticles has promising antitumor activity [28].

Xiang-Ping Meng *et al*., 2016 showed that incubation HepG2 and Huh7 cell lines and EC9706 cells with lipid nanoparticles containing berberine lead to a significant reduction of cancer cells growth. In fact, in this study the anticancer property of lipid nanoparticles containing berberine against HCC was confirmed [33]. A research group was studies the anti-tumor property of Janus magnetic mesoporous silica nanoparticles as a delivery system for berberine. This nanoparticles had properties such as non-identical surface, good magnetic strength, proper drug loading, obvious endocytic ability and prominent cytotoxic.

Incubation of HCC cells with mentioned nanoparticles led to reduction of tumor cells due to proper drug delivery to target location. Meanwhile, drug distribution was not obvious in hepatocytes. In addition, outer surface of the magnetic had pivotal role to entry drug into cell due to magnetic property [34]. The use of lipid nanoparticles as a suitable delivery system increases anticancer activity berberine against hepatocarcinoma cell line H22 because treatment with nanoparticles containing berberine reduced tumor growth significantly [35].

Silica nanoparticles have pivotal role to increase anti-tumor activity of berberine. According to a study conducted by Halimani and colleagues in 2009, the effect of the nanoparticle-containing berberine against human cervical carcinoma cell line (HeLa), hepatocellular carcinoma cell line (HepG2) and embryonic kidney cell (293T) were assessed. The results showed that the antitumor activity of nanoparticles containing berberine is more than free berberine form. This effect occurred through cell cycle arrest in G1 phase. In addition, apoptosis induction was another reason to reduce tumor mass [28]. Selenium is a vital element in maintaining of body health and recent studies have been confirmed its anticancer property against prostate and colorectal cancers in animal models [36 - 38]. These observations were unexpected, daily intake of selenium as a supplement can be beneficial to all people, and it was found reduction of cancer after treatment with selenium only in people with plasma selenium level 1.53 µmol/l before their entering to clinical trials [39]. Selenium performance is reflected by selenoproteins and its metabolites that both are tumor regulators [40, 41].

In fact, it has been found at least 25 different selenoproteins with especial antioxidant activity while selenium metabolites induce reactive oxygen species [42]. Selenium in lethal doses leads to abrogation of cancer cells through induction of apoptosis and cell cycle arresting [43 - 45]. However, it has been showed neurological effects at high doses so that a daily intake of selenium supplements contain (60 - 120 µg/kg body weight) leads to mental disorders [46]. Today, advances in nanotechnology facilitates to develop new methods for embedding of selenium in nanomaterials that have significant potential for use in medical field, diagnosis of diseases, toxicology and treatment [47].

In fact, in order to increase of efficiency of selenium, can use nanoparticles because they can control selenium releasing for reduction of toxic effects [48]. Chen *et al*., 2008 demonstrated that selenium nanoparticles with polysaccharides Undaria pinnatifida induce apoptosis in human melanoma cell line (A375) through increase of oxidative stress and mitochondrial dysfunction [49]. In a study, it was found that selenium nanoparticle inhibits growth of prostate cancer cell line (LNCaP) and leads to apoptosis induction by activation of caspases.

In addition, it resulted in down regulation of androgen receptor, increase of Akt kinase phosphorylation and androgen receptor depended on Akt and Mdm2 degradation by proteasome pathway [50]. Yazdi *et al*., 2012 reported that due to anticancer effects of selenium nanoparticles against cell line 4 T1 and stimulation of Th1cytokine such as IFN-γ and IL-12 in mice's spleen suffered from breast cancer, therefore it can be a promising drug to control and reduction of breast cancer [51]. Reduction of growth of cell lines MDA-MB-231 and HeLa occurs after treatment with selenium nanoparticles. Meanwhile, this nanoparticle arrest cell cycle in S phase after incubation in HeLa cells. MTT test confirms reduction of cancer cells after treatment.

According to this study, selenium nanoparticle is a good drug for cancer treatment [52]. Nanoparticles Selenium enriched by strain *Lactobacillus plantarum* is effective in stimulating of immune system against breast cancer induced in mice because it leads to increase of inflammatory cytokines levels such as IFN-γ, TNF-α and IL-2 as well as increase of natural killer cells (NK cell) activation [53]. Gallic acid is considered as an anti-tumor natural compound found in plants such as grapes, pomegranates, vegetables, rose and green tea [54]. However, it is a safe drug due to lack of toxic effects on fibroblast and endothelial cells [55].

To exposure compounds with anti-tumor property in a suitable delivery system greatly reduces their toxic effects lead to their accurate transferring to desired location. Nano-carriers such as nano-particles and liposomes can be perfect candidate for this work [56]. Despite the favorable effects of gallic acid in reduction of oxidative stress, but it is not desirable pharmacokinetic property due to slight bioavailability that leads to limiting its use in the treatment of diseases. Use of nanoparticle is one of the strategies to solve this problem. In a study, it was found that chitosan-glycerol phosphate nanoparticle could be a delivery system for gallic acid so that it dramatically increased antioxidant effect of gallic acid [57]. Gallic acid is a compound with antidepressant property due to reduction of glutathione level and improvement of oxidative status in the central nervous system. In fact, the use of nanoparticle was very helpful in promotion of its antioxidant property and subsequently depression reduction [58]. Silica nanoparticle is used to transfer gallic acid due to have high stability, low toxicity, therefore it can deliver hydrophilic and hydrophobic compounds such as wide range of drugs, biological active compounds and proteins [59]. Nanoparticles increase cytotoxic activity of gallic acid against cell lines Caco-2 cells [60]. The use of nanoparticles to deliver gallic acid into cancer cells improves its anticancer activity.

In fact, the treatment of cervical cancer cell lines (CaSki and HeLa) with gallic acid covered by fifteen-nanometer spherical gold nanoparticles result in tumor growth inhibition, apoptosis induction without significant cytotoxic effect in normal cells [61]. Rattanata *et al*., 2014 found that transfer of gallic acid into adenocarcinoma cell lines (M213, M214) by gold nanoparticles lead to increase of tumor growth inhibition and improvement of gallic acid efficacy in association with apoptosis induction [62]. Polymeric nanoparticles formed from chitosan as a delivery system to transfer gallic acid have good solubility under neutral and basic conditions. In addition, antioxidant and cytotoxic activity of this nanoparticle against cell line (Caco-2) related to colon cancer was showed that they have potential ability to abrogate cancer cell lines due to obvious drug delivery to tumor site [63]. Zhou *et al*., 2016 reported that nanoparticle Se/Rualloy with gallic acid is an anti-cancer drug and induces apoptosis HeLa cell line. Moreover, it inhibits migration and transfer of cancer cells by inactivation of matrix metalloproteinases such as MMP 2 and MMP-9 [64].

Melatonin (N-acetyl 5-methoxy Tryftamyn) is a hormone secreted by pineal gland that involved in sleep-wake cycle. Darkness stimulates its secretion and stimulation of retinal neurons by light suppresses its secretion [65]. During day, its secretion amount is 10 pg/ml but it is increased at 9 pm and reached the greatest of its level during 2 - 4 am (70 - 100 pg / ml) [66]. For clinical purposes, artificial melatonin has same functional endogenous melatonin but it has not significant pharma-cokinetic property and its half-life is very low [67]. Its bioavailability is very low and it easily excreted from the body due to liver metabolism [68]. Use of a delivery system is essential for melatonin and nanoparticle can be a good candidate to solve this problem [69].

In fact, the nanoparticles can cover hydrophilic and lipophilic compounds in themselves and be helpful in their transfer into the desired location [70]. In a study, it was showed that use of lipid nanoparticle for transfer of melatonin resulted in improvement of melatonin plasma levels that led to increase of its efficacy [69]. According to a study conducted by Topal *et al*., 2015, it was proven that melatonin combined with nanoparticles 2-hydroxypropyl-β-cyclodextrin in a complex reduces growth rate in cell line MG-63 due to cell cycle arresting in G2/M phase instead of S phase because the mentioned complex increased the stability and releasing of melatonin [71].

In another study, it has been showed that the use of poly (d, l-lactide-co-glycolide) nanoparticle for transfer of melatonin leads to increase of anticancer activity against cell lines MG-63 so that this polymeric system could improve conditions for chemotherapy against osteosarcoma [72]. The most common types of nanoparticles used for drug delivery are polymer nanoparticles, solid lipid nanoparticles (SLNs), crystal nanoparticles, liposomes, micelles, and dendrimers **Fig. 1A**. Each of these nanoparticles has its own advantages and disadvantages as drug delivery vehicle. Polymeric nanoparticles have been the most tested in combination with natural products. Poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), poly-l-lactic acid (PLA), polycaprolactone (PCL), and chitosan are the most common polymers used due to their bio-compatibility, biodegradability, and the fact that they are easy to functionalize **Fig. 1B**.

Chitosan itself is a natural polymer that has gained attention recently in applications with natural product delivery [73 - 79]. There are two types of polymeric nanoparticles: nanocapsules and nanospheres **Fig. 1C**. Nanocapsules contain a drug-filled core, which is surrounded by a polymer membrane. The nanospheres are porous and the drug is uniformly distributed among the pores [80]. To overcome some limitations in the old-generation SLNs, liquid lipid has been incorporated into the solid structure; resulting in nanostructured lipid carriers **Fig. 1D**. Three types of lipid nanoparticles have been described: an imperfect type, an amorphous type, and a multiple type. The imperfect type contains spatially different lipids and allows for increased drug-loading capacity. The amorphous type mixes solid lipids with special lipids, such as medium-chain triglycerides, to prevent crystallization and drug expulsion during storage. The multiple-type nanoparticle has added liquid lipids that increase the solubility of many drugs and decrease drug expulsion during storage. Structures of selected natural compounds discussed in this review are shown in **Fig. 2**. Relevant physicochemical properties of the selected compounds are listed in **Table 1**.

TABLE 1: PHYSICO - CHEMICAL PROPERTIES OF SELECTED NATURAL COMPOUNDS

Natural Compound	Partition coefficient (logP)	Polar surface area/Molecular surface area Å^2
Apigenin	2.71	86.99/326.60
Baicaelin	2.71	86.99/325.74
Berberin	-1.28	40.8/473.39
Caffeic acid	1.53	77.76/226.17
Caffeine	-0.55	58.44/269.15
Catechine	1.80	110.38/373.00
Cinnamaldehyde	1.98	17.07/194.07
Curcumin	4.12، 3.29[b]	93.06/194.07
Epigalloctechin gallate	3.08	197.37/556.67
Ellagic acide	3.32	133.52/319.89
Epicatechin	1.80	110.38/373.01
Eugenol	2.61	29.46/257.78
Gambogic acid	7.78	119.36/906.97
Genistein	3.08، 3.04[c]	86.99/325.45
6-Gingerol	3.62	66.76/507.44
Hydroxytyrosol	0.89	60.69/230.61
Kaempferol	2.46، 3.11[c]	107.22/337.38
Luteolin	2.40	107.22/337.39
Morin	2.16	127.45/348.34
Naringenin	2.88، 2. 6[c]	86.99/351.09
Oleuropein	0.11	201.67/727.25
Paeonol	1.72	46.53/251.92
Quercetin	2.16، 1. 82[c]	127.45/348.11
Resveratrol	3.40	60.69/308.38
Rosmarinic acid	3.00	144.52/456.21
Salidroside	-0.58	119.61/426.44
Salvianolic acide B	pH dependent [d]	N/A
Silibinin	2.63	155.14/614.71
Tanshinone l	4.00	47.28/368.83
Taxifolin	1.82	127.45/367.80
Thymoquinone	2.55	34.14/245.97
Tyrosol	1.19	40.46/219.74
Ursolic acid	6.58	57.53/795.27

Notes: [a]LogP and surface area values are obtained from source http://www.chemicalize.org unless specified; [b]Data from Grynkiewicz G *et al*., 2012; [c]Data from Rothwell JA *et al*., 2005. [d]Data from Li J *et al*., 2013.

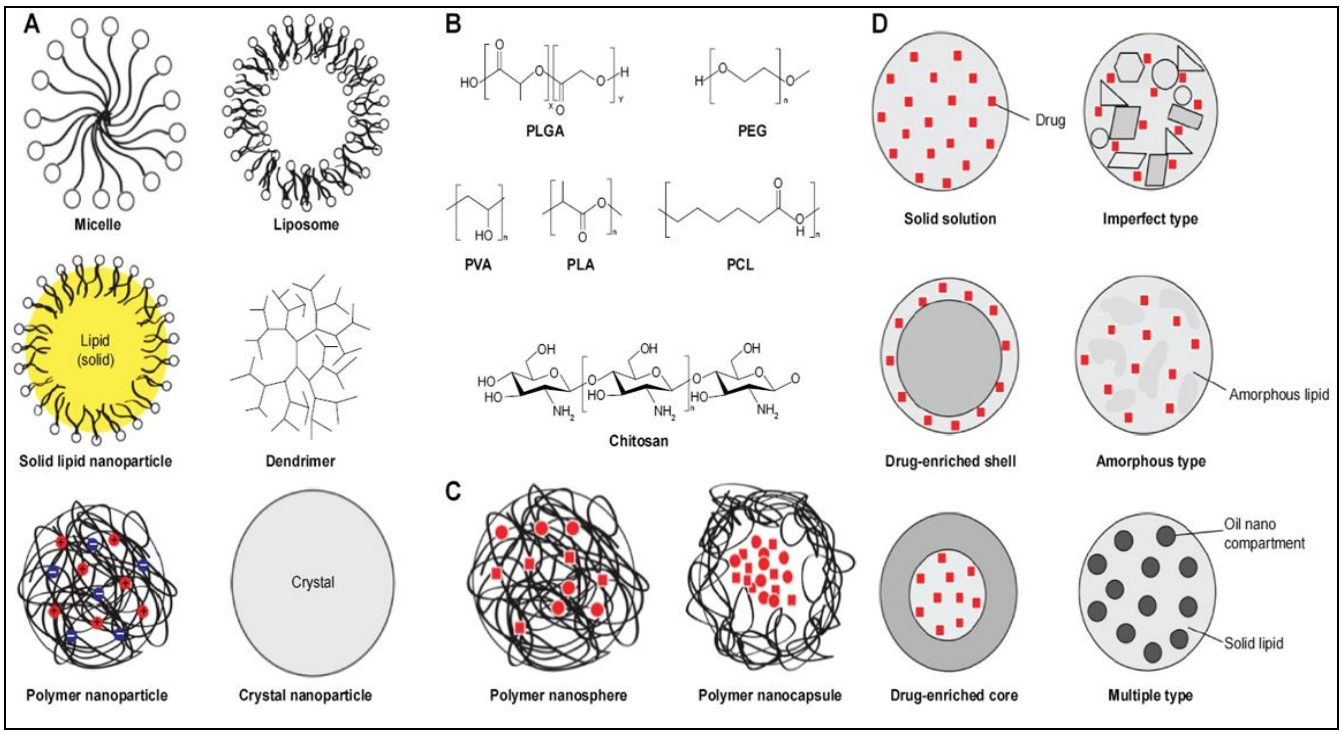
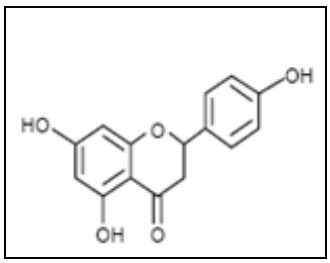
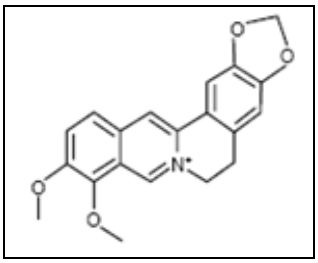


FIG. 1: SCHEMATIC REPRESENTATION OF NANOPARTICLES

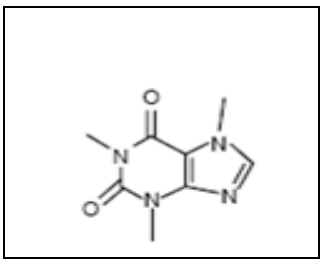
Notes: (A) Graphical representations of the most common types of nanoparticles. Charges in polymers are indicated as red and blue circles for some polymer nanoparticles. (B) Chemical structures of the most common types of polymers used in polymer nanoparticles. (C) Graphical representations of the two types of polymer nanoparticles. The drugs incorporated are shown in red. (D) Drug-incorporation models in solid lipid nanoparticles (left) and types of nanostructured carriers (right). Abbreviations: PLGA, poly (lactic-co-glycolic acid); PEG, polyethylene glycol; PVA, polyvinyl alcohol; PLA, poly-l-lactic acid; PCL, polycaprolactone.



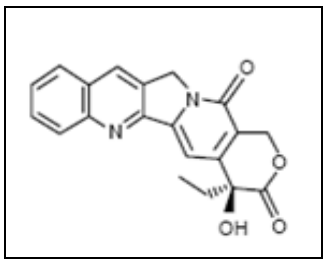
EPIGENIN



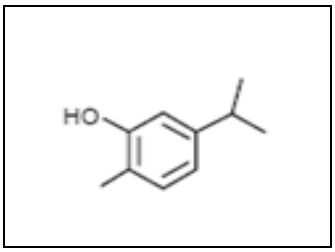
BERBERINE



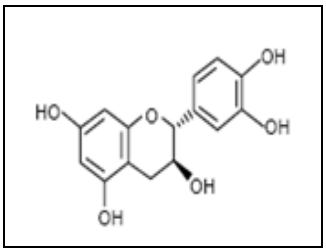
CAFFEINE



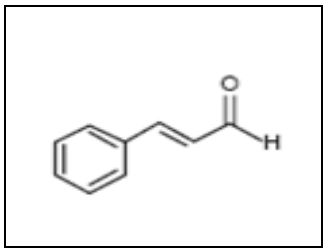
CAMPTOTHECIN



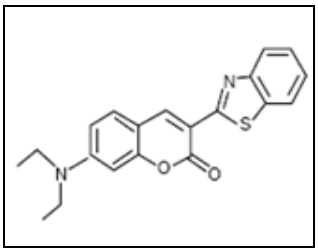
CARVACROL



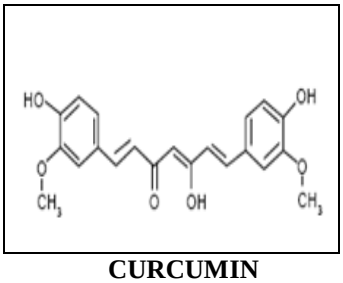
CATECHIN



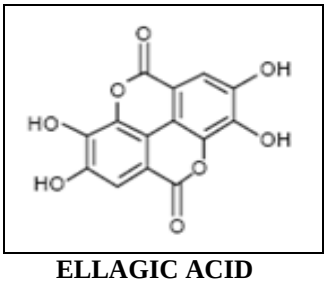
CINNAMALDEHYDE



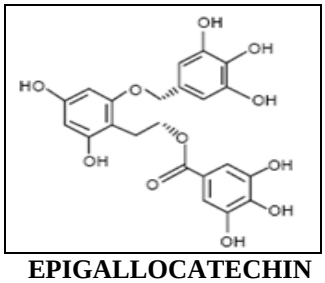
CAUMARIN-6



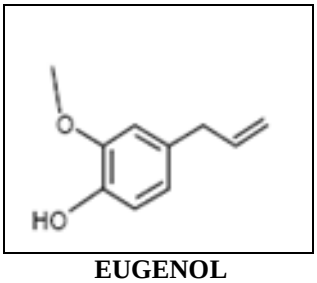
CURCUMIN



ELLAGIC ACID



EPIGALLOCATECHIN GALLATE (EGCG)



EUGENOL

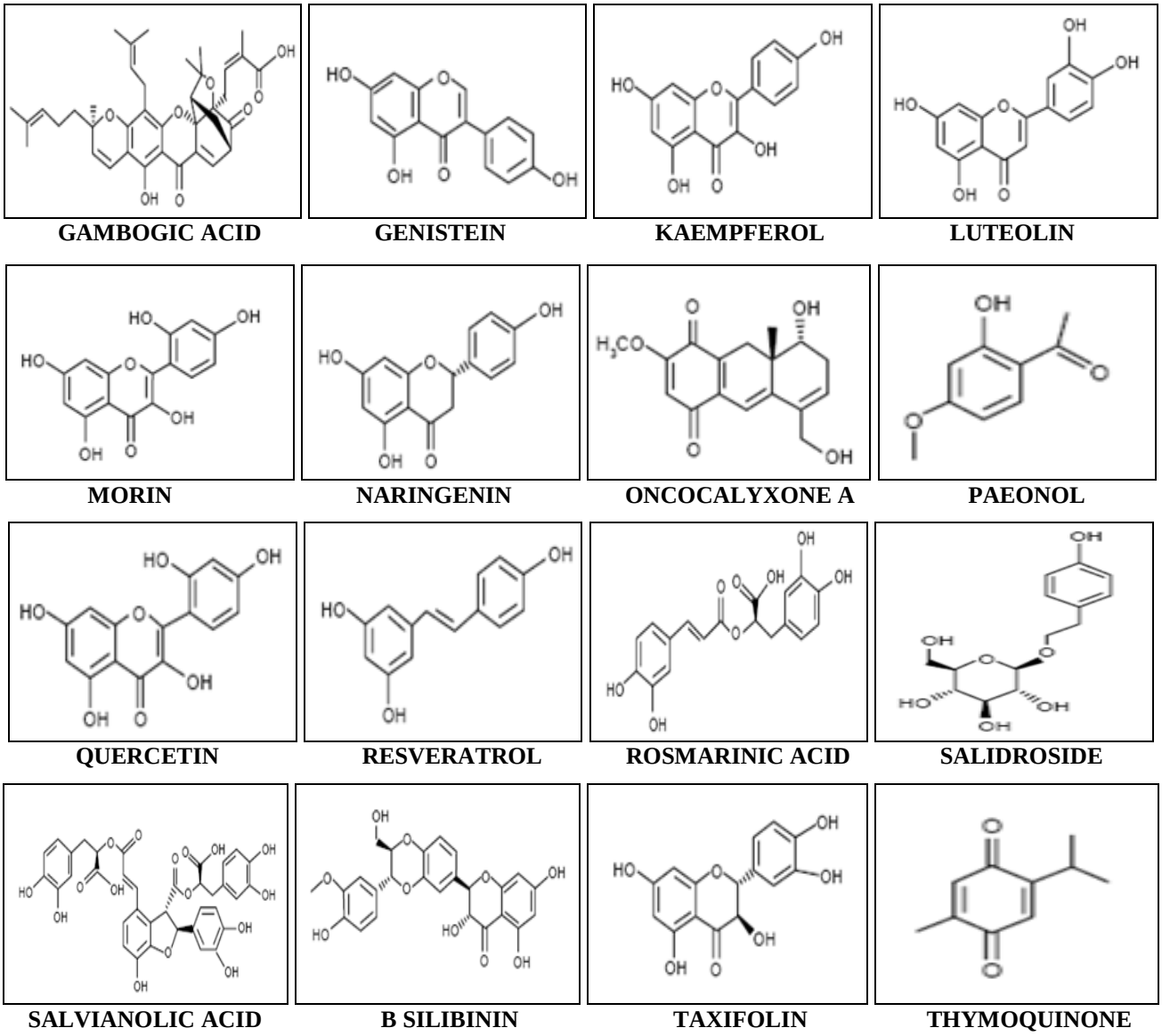


FIG. 2: CHEMICAL STRUCTURES OF SELECTED NATURAL COMPOUNDS DISCUSSED IN THIS REVIEW

Bioavailability: Nanoparticles can improve the effectiveness of natural compounds in disease treatment and prevention by increasing their bioavailability. Many of the studied natural compounds, such as curcumin, resveratrol, and EGCG, are highly lipophilic **Table 1**. Highly lipophilic compounds are not ideal for drug delivery because they do not dissolve well in the bloodstream. These compounds have a low bioavailability, and therefore large quantities of the compounds must be administered in order to achieve the desired therapeutic effects. The large dose size of these compounds can lead to acute toxicity or low patient compliance. Just encapsulating these highly lipophilic compounds can improve their water solubility and efficiency. Celia *et al.*, [81] have found that bergamot essential oil, which has anticancer properties, when encapsulated in liposomes, showed improved solubility of the drug and led to increased cell death *in vitro*. This was also true for nanoemulsified berberine.

The nanoberberine was added to a phosphate buffer and in 45 minutes, 85% of the compound dissolved, compared to only 60% of the free berberine in the same time period. Other classes of natural compounds, such as tannins and terpenoids, are highly hydrophilic. These compounds have low bioavailability because they cannot cross biological membranes. In both of these cases, incorporating the natural compound into a nanoparticle can improve the bioavailability and lower the dose needed to obtain a therapeutic effect. **Table 2**

provides several examples of nanoparticle formulations and adjuvants that increase the bioavailability (drug concentration in plasma) of selected natural compounds. Curcumin, a diarylheptanoid derived from turmeric, has generated immense interest as a lead compound against a variety of health conditions, including cancer, inflammation, microbial infection, angiogenesis, amyloidosis, wound healing, and alleviation of morphine tolerance. However, poor bioavailability is a major limitation to the therapeutic utility of curcumin in clinical trials.

TABLE 2: COMPARISON OF PLASMA CONCENTRATIONS OF NATURAL COMPOUNDS WITH THE USE OF NANOPARTICLES OR ADJUVANTS AND IN FREE DRUG FORM

Natural compound	Nanoparticle or adjuvant	Dose	Plasma concentration		Mixture (free drug mixed with empty nanoparticle)
			Encapsulated by nano-particle (or with piperine)	Free drug	
Apigenin	Carbon nanopowder solid dispersion	60 mg/kg body weight [82]	3.26 µg/mL	1.33 µg/mL	1.43 µg/mL
Curcumin	Liposome	100 mg/kg body weight [83]	319.2 µg/L	64.6 µg/L	78.3 µg/L
Curcumin	Solid lipid nanoparticle	50 mg/kg body weight [84]	14.29 µg/mL	0.292 µg/mL	N/A
Curcumin	PLGA nanoparticle	100 mg/kg body weight [85]	6.75 µg/mL	1.55 µg/mL	N/A
Curcumin	Piperine as adjuvant in rats	2 g/kg curcumin and 20 mg/kg piperine body weight [86]	1.8 µg/mL	1.35 µg/mL	N/A
Curcumin	Piprine as adjuvant in humans	2 g/kg curcumin and 20 mg/kg piperine body weight [86]	0.006 µg/mL	0.18 µg/mL	N/A
EGCG	Piprine as adjuvant in mice	163.8 µmol/kg EGCG and 72.2 µmol/kg piperine body weight [87]	0.66 µmol/L	0.32 µmol/L	N/A
Taxifolin	Nanoparticles liquid antisolvent precipitation	50 mg/kg body weight [88]	13.5 ng/mL	1.3 ng/mL	N/A

Abbreviations: EGCG, epigallocatechin gallate; N/A, not available; PLGA, poly (lactic-co-glycolic acid)

CONCLUSION: In recent decades, it has been examined the ability of nanoparticles in drug delivery. These studies confirmed that nano-particles could be considered as good strategy in order to improvement of pharmacodynamic and pharmacokinetic of drugs. In addition, use of nanoparticles at *in vivo* models confirms that they can maintain bioavailability of drugs in blood circulating system. Moreover, they can control drug releasing. It has been used different polymers to formulate nanoparticles in order to promotion of their therapeutic effect and reduction of their side effects.

In this review, we showed that nanoparticle could be considered as good carriers for bioactive compound. Therefore, in order to achievement of better findings should be more attention to nanoparticles in further studies.

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