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INTERACTION OF BIOACTIVE COMPOUNDS WITH CERAMIC MATERIALS – A REVIEW

Gertrud-Alexandra PALTINEAN[1], Gheorghe TOMOAIA[2,3], Levente-Zsolt RACZ[1], Aurora MOCANU[1], Maria TOMOAIA-COTISEL[1,3]

Abstract. *This review examines the interaction between silymarin (SIL) and other plant-based bioactive compounds such as curcumin (CCM), piperine (PIP), resveratrol (RES), and icariin (ICA). Their combination revealed synergistic effects on colon (HCT116), breast (T47D) tumor cells, hepatocellular carcinoma, and periodontal disease. The review also addresses the interaction between these plant extracts with ceramic materials such as hydroxyapatite (HAP) and carotenoids with concrete examples of biomedical applications. Silymarin's interaction with chemotherapeutic drugs (doxorubicin-DOX, paclitaxel-PCT and 5-Fluorouracil-5-FLU) and gold nanoparticles-GNPs and silver nanoparticles-SNPs is also debated. All these combinations can form composites of major importance in the biomedical field and to contribute significantly to orthopedic surgery where materials are needed for implants that face severe infections. This short review highlights the variety of multifunctional nanoparticles that open new opportunities in cancer treatment and the need to use the Langmuir Blodgett Technique that mimics the biological membrane and provides rich medical information.*

Keywords: Silymarin, bioactive compounds, hydroxyapatite, carotenoids, chemotherapeutic drugs, gold nanoparticles, silver nanoparticles

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1. Introduction

Plants and their role in human health have recently received special attention. They have in their portfolio a wide range of biological activities with the role of protecting the organs and tissues of the body against various diseases. By using them, it has been possible to maintain a balance between controlling morbidity and regaining health. The medical system is exposed to pathogens. This means maintaining health is difficult for those hospitalized for either treatment or chirurgical procedures. Science through its research activities and experimental results highlights a first step in prolonging health by preventing disease and efficacy against widespread communicable diseases. In this sense, some bioactive compounds, seen in figure 1, fight against diseases since ancient times.

[1]Babes-Bolyai University, Faculty of Chemistry and Chemical Engineering, Research Centre of Physical Chemistry, 11 Arany Janos Str., RO 400028, Cluj-Napoca, Romania
[2]Iuliu Hatieganu University of Medicine and Pharmacy, Department of Orthopedic Surgery, 47 General Traian Mosoiu Str., RO 400132, Cluj-Napoca, Romania
[3]Academy of Romanian Scientist, 3 Ilfov Str., District 5, RO 050044, Bucharest, Romania
[*]Corresponding author: Maria Tomoaia-Cotisel, mcotisel@gmail.com

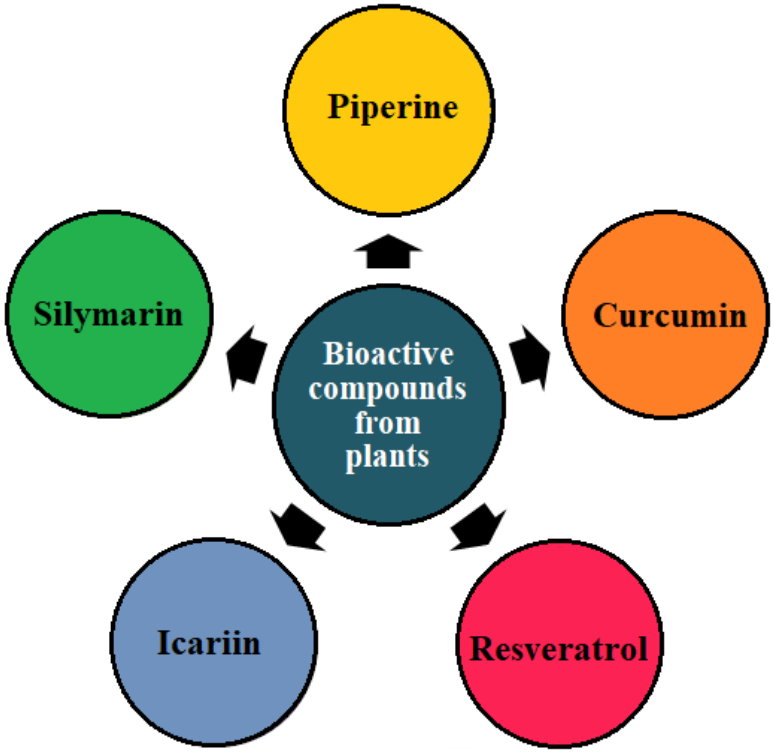

Fig. 1. Bioactive compounds from plants

The previous study carried out by our team showed a rich biological activity and therapeutic potentials of piperine, curcumin, resveratrol, and icariin. Also, we discussed the interaction between them, the interaction with chemotherapeutic drugs, the interaction with silver and gold nanoparticles and the beneficial effects on health, especially applications in cancer cell lines [1].

In the present study, all these proactive compounds and silymarin have in common their anticancer and anti-inflammatory activities. However, the most studied at present is the anticancer activity. Cancer is a relentless disease that does not consider age and involves the abnormal development of body cells. It can be established in any type of organ such as pancreas, liver, lungs, breast, ovaries, stomach, rectum, etc. This disease can occur either inherited or due to multiple environmental factors and socio-industrial activities in which man lives. Examples that can lead to cancer are smoking, alcohol, poor lifestyle, unhealthy diet, exposure to toxic substances. From this point of view, these compounds could become the main pawns in the treatment of this condition and, why not, the definitive eradication in a stage in which the disease is not advanced enough so that the tissues respond effectively to the treatment**.**

Curcumin (CCM) is a bioactive compound produced by *Curcuma Longa* and is currently used as a dye in the food industry. The solubility of curcumin is poor and the rate of absorption into the body is also low. Due to its rich biological activities, it has been used since ancient times in traditional Chinese, Indian and Ayurvedic medicine and is widely used in biomedical applications. In the case of anti-cancer activity curcumin downregulates the production of pro-inflammatory cytokines TNF-α and IL-1β and inhibits the activation of transcription factors nuclear NF-kB [2]. Also, it is known to induce apoptosis in prostate cancer cells but also to prevent the progression of this cancer [3]. This proactive compound can form innovative composites and complexes with applications in medicine and in this sense facilitates the understanding of the mechanisms of action during application [4-9].

Silymarin (SIL) is the main component in the plant *Silybum marianum*, also used since ancient times in the treatment of liver diseases (cirrhosis, jaundice, hepatitis) and biliary diseases [10-12]. It is a compound rapidly metabolized, absorbed and eliminated within six hours. It is not soluble in water but can be administered as an encapsulated standardized extract [13, 14]. SIL has a rich biological activity such as anticancer, antioxidant, anti-inflammatory, anti-diabetic, anti-lipemic, anti-osteoporotic, anti-viral, anti-arthritic [11, 13]. It is widely studied in the treatment of cancer because it inhibits tumor growth and modulates signaling pathways such as NF-β, EGFR-MAPK / ERK 1/2 and IGF. In the case of bladder carcinoma, silymarin stops the G2 / M phase and modulates the cascade of the cyclin CDK1-CDK. It is reported to activate caspase 3, resulting in inhibition of the growth and apoptotic death of TCC cells [11, 15]. In hepatocellular carcinoma, silymarin inhibits the increase in b-catenin, inhibits mitochondrial membrane potential of HepG2 cells and modulates the activity of CDK-2, CDK-4, and CDC-2 kinase [16]. In prostate cancer silymarin inhibits the growth of cancer cells both in vitro and in vivo and modulates MAPK, ERK 1/2, and IGF signaling pathways [17]. In the case of A549 cells from lung cancer, silymarin inhibits phosphorylation of ERK 1/2 and reduces the level of MMP-2 and u-PA [18].

It is known from literature studies that **piperine (PIP)** inhibits the growth of human prostate cancer cells such as LNCaP, PC-3 and DU145 in a dose-dependent manner and induces the cell cycle arrest at G0/G1-phase ($P < 0.05$). It also reduces the viability of osteosarcoma cells (HOS, U2OS) in time and dose-dependent manners and exposure to piperine causes G2/M phase arrest of the cell cycle. On the human bone marrow (K-562 leukemic cells) piperine induces anticancer effects. The fight against tumor cancer lines is in a dose-dependent manner, in which the mechanism of action is associated with mitochondrial

damage, increased reactive oxygen species and expression of key proteins (Bcl - 2, Bax, Cyt - c, Caspase - 9 and Caspase - 3) affected [19-22].

In the case of bladder cancer, **resveratrol** (**RES**) exerts a significant cytotoxic effect and induced cellular apoptosis of T24 cells in a dose- and time-dependent manner. Also, the treatment of T24 cells with resveratrol caused G1 phase cell cycle arrest [23]. Resveratrol has low bioavailability and is known to act synergistically with hemotherapeutic drugs to increase their anti-cancer effects. It was demonstrated that resveratrol sensitized chemotherapeutic drugs resistant to cancers [24, 25]. Although the mechanism of action of resveratrol is not fully elucidated it has been shown that it directly inhibits the proliferation of pancreatic cancer cells in a dose- and time-dependent manner. Also, it can induce apoptosis and cell cycle arrest, enhances the chemo-radio-sensitization and can affect diabetes mellitus [26].

As for **icariin** (**ICA**), it has anticancer activity in lung cancer. In vivo experiments have shown a decrease in H1975 cell proliferation and in vitro this reduces A549 and H1975 cell proliferation in a dose and time dependent manner [27]. In the case of human esophageal carcinoma cells (KYSE70 cells), icariin causes the cell cycle to stop in the G2 / M phase [28]. Icariin, a hydrolytic product of icariin, has also been widely studied in traditional Chinese medicine. Nowadays, due to the multiple pharmacological activities, icariin has increased the interest of researchers for antitumor activity. In the case of different types of cancer such as human endometrial cancer and glioblastoma multiform cell lines, icariin induces G1 phase arrest. In lung cancer, it causes S phase arrest while in oral squamous cell carcinoma (OSCC), colon cancer and renal cell carcinoma cell lines; it arrests cell cycle in G1/S phase [29].

Given that technology and nanoscience have reached a high level of development, the World Health Organization (WHO) estimates that about a third of all existing cancers could be prevented [30, 31]. According to the WHO globally, in 2018, 18.1 million people were diagnosed with cancer, of which 9.6 million died. The most common cancers are lung (11.6%), breast (11.6) and colorectal (10.2%). Early diagnosis is the best way to prevent the progression of this disease followed by treatment that may involve chemotherapy and surgery. In the case of cancer that occurs in children, the most common is bone marrow leukemia and lymphatic system cancer. The cause of the emergence is not yet understood, but at the level of current knowledge it is known that it is not preventable.

Thus far, we have highlighted the characteristics of the bioactive compounds applied individually; in the following we will discuss the synergistic effect obtained between Silymarin and these compounds. This herbal therapy

enhances beneficial activity in treating diseases and involves mechanisms of action responsible for stopping cancer at various stages of development.

2. Silymarin interaction with proactive compounds from plants

Literature studies show that there is a synergistic effect between the ***silymarin and curcumin***. A. Montgomery and colleagues studied the effect of this combination using colon cancer cell lines DLD-1, HCT116 and LoVo. They showed that the combined treatment on these cancerous lines inhibited cell proliferation and increased apoptosis. As a conclusion of their study, the combination of CCM + SIL leads to higher level of inhibition of cancer cell much more effectively than if applied individually [32].

A study conducted by N. Abdel-Magied highlights the possible curative role of combined therapy against nephrotoxicity induced by gamma-rays in rats. The irradiated rats treated with combined therapy revealed a significant decrease of malondialdehyde, H_2O_2 and advanced oxidation protein products and a significant increase of GSH and total antioxidant capacity. They observed additive effects on the level of Interleukin 18, tumor necrosis factor alpha, C-reactive protein, Bax, factor-related apoptosis and the activity of Casp-3 by 58%, 58%, 41%, 47%, 64%, 31%, respectively associated with an increase of Bcl2 level by 122%. The additive effect is manifested by a decrease of malondialdehyde, hydrogen peroxide and advanced oxidation protein products on irradiated rats. They conclude that combination could be used as a medication for protection of patients during radiotherapy [33].

M. M. Ahmad et al show that paracetamol treatment caused liver damage. Individual application of CCM and SIL produced hepatoprotective effects due to antioxidant activities. They conclude that CCM is more effective than SIL at protecting the liver against paracetamol toxicity [34]. T47D breast cancer cell line was treated with Silibinin+CCM mixture. This mixture has an inhibitory effect on hTERT gene expression in a dose-dependent manner and the real-time PCR results show a significant decrease in hTERT expression [35].

Silymarin and resveratrol combination was highlighted in a study conducted by A. Farzanegan and coworkers. The obtained results show antihistamine effects on human gingival fibroblasts. They evaluate the cell viability in 24h and 48h after treatment with 50/100 and 100/200 μg/ml of silymarin/resveratrol in the presence of histamine (10 μg/ml). The results showed a significant reduction in viability with a combination of 100 μg/ml silymarin and 200 μg/ml resveratrol in 48 h. This concentration was found to decline the secretion of IL-8 and TPA-1 while the combination of resveratrol/silymarin 100 μg/ml and 50 μg/ml demonstrated a considerable drop in the secretion of all detected factors (IL-8, IL-6, TPA-1, and TNF-α). This kind of combination can be useful as a therapeutic

agent for treatment of periodontal diseases [36, 37]. In their study, W.-C. Hsieh et al concluded by their study that the Silymarin/resveratrol combination presents a synergistic effect on the reduction of the hepatocellular carcinoma in a mouse model and can be a potential agent for the prevention of HCC in high-risk chronic hepatitis B virus carriers [38].

Regarding the combination of ***piperine and silymarin,*** R. Shukla and collaborators, evaluate the hepatoprotective activity against D-galactosamine induced liver damage in albino rats. The results after treatment with this combination show a protective activity on liver against the injury induced by D-galactosamine [39]. S. Javed et al suggest by their studies that SIL + PIP might have a synergistic effect and might have hepatoprotective and antioxidant activity [40].

Regarding **ICA and SIL**, there is not enough information to evaluate the action mechanism.

3. Silymarin and chemotherapeutic drugs

In our previous study we highlighted the interaction of plant extracts with chemotherapeutic drugs (doxorubicin – DOX, paclitaxel – PCT and 5-fluorouracil-5-FLU) and separately with gold and silver nanoparticles. Silymarin can also interact with chemotherapeutic drugs to help treat different types of cancer and other conditions. Studies in the literature have investigated the genotoxic and cytotoxic effects of ***SIL and DOX*** applied individually and in combination on the HepG2 cell line for 24 hours and 48 hours. E. Yurtcu et al noticed that the individual application of the two is more effective than their combination in this case. They say that after 24 hours the two treatments caused DNA damage, while after 48 hours the genotoxic damage was stronger with doxorubicin than with SIL. The combination of the two did not have significant results but more clinical trials are needed to see the effect on other cancer [41]. Another study conducted by N. Patel et al show that SIL reduced DOX hepatotoxicity and associated apoptotic and necrotic cell death. Also, SIL can modulate changes in Bcl-xL and p53 expression [42]. It is known that doxorubicin can cause heart, liver, and kidney toxicity if it is administered more than necessary. E Cecen and his research group demonstrate that silymarin protected these organs from doxorubicin toxicity [43]. F. Gheybi and coworkers combined the SIL + DOX liposomes in 4T1 breast cancer cells at 100 and 300 molar ratios of the two drugs. The results show synergistic growth-inhibitory effects at this molar ratio. They concluded that the successful combination of the two medications plays an important role which determines the final response following treatment [44]. The principal compound from silymarin is silibinin and A. K. Tyagi demonstrated that silibinin strongly synergized the growth-inhibitory effect of doxorubicin in prostate carcinoma DU145 cells with a strong G2-M

phase arrest in cell cycle progression [45]. In the case of **paclitaxel (PCT)**, another chemotherapeutic drug, silibinin enhanced the therapeutic potential of paclitaxel against human gastric cancer SGC-7901 cells [46]. O. Molavi et al, evaluate the synergistic effect of silibinin and DOX and ***silibinin with PCT*** to in breast cancer cells line (MDA-MB435 and MCF-7) and the results show better effects of silibinin - DOX in MDA-MB435/WT cells then in silibinin + PCT in MCF-7/WT. They observed that silibinin increase the cytotoxic effect of DOX and PCT [47].

S. Patel et al evaluated the synergy effect of ***Silibinin and 5-Fluorouracil*** that inhibited cell proliferation of CD44+ subpopulation of human colon carcinoma (HCT 116 cells) at lower concentrations. Also, silibinin+5-FLU inhibit the cancer stem cell population and significantly reduce the bulk tumor cells [48]. SIL can play a protective role in 5-FLU induced oxidative stress in liver and kidney tissues by eliminates 5-FLU toxicity. The study concluded that this kind of effect is due to the powerful antioxidant and anti-inflammatory properties of SIL [49].

4. Silymarin and Metallic Nanoparticles (gold nanoparticles-GNP, silver nanoparticles-SNP)

The design of composites based on gold nanoparticles (GNPs) and silver nanoparticles (SNPs) functionalized or conjugated with silymarin opens new areas of research in medicine. These metallic nanoparticles are among the most studied in the literature due to their properties, biological activities, photocatalytic hydrogen production and photocatalytic activity toward organic compounds [50, 51]. Also have ability to bind various biomolecules such as amino acids, proteins, anesthetics, antibiotics [52-73]. In this way, they managed to acquire a variety of biomedical applications, including the treatment of cancer and infections that occurred after postoperative surgery in orthopedic and dental surgery. Among the metallic nanoparticles, we remember also platinum nanoparticles that are also useful in biomedical applications but this rare metal are too expensive, so he received less attention [74, 75].

S. Clichici and collaborators loaded the ***gold nanoparticles with silymarin***. They observed an improved liver function and reduced cholestasis. The administration of silymarin loaded gold nanoparticles in liver function, significantly decreased the aspartate aminotransferase level (ASAT) in the serum. They concluded that the effect of gold nanoparticles coated with silymarin was significantly better than silymarin alone [76]. On the other hand, S. Staroverov et al examined the silymarin conjugated colloidal gold nanoparticles to see the liver protecting activity. The results show that conjugate administration interfered with glutathione depletion in hepatocytes and stimulated monocyte macrophage function. So, they conclude that SIL-GNP conjugate is possible to be used as a potential liver-protecting drug [77]. A. S. Abdullah and coworkers prepared

Silymarin conjugated gold nanoparticles to improve SIL bioavailability and release for potentiating its antifibrotic action in a rat model intoxicated with CCl_4. They concluded that silymarin conjugated gold nanoparticles may induce anti-fibrosis effects by enhancing the hepatic expression of the protective microRNAs [78]. In the case of SNP, R. Mohammadinejad synthesized silver nanoparticles using S. marianum extract that can lead to mediate colloidal spherical nanoparticles ranging in size from 1 to 25 nm. Silymarin extracted from seed and fruit is showed to be a good source for synthesis of stable SNPs with simple process of synthesis, low cost and eco-friendly [79, 80].

5. Silymarin and bioactive compounds interaction with hydroxyapatite

Hydroxyapatite is a calcium phosphate found in the hard tissues of the human body such as bones and teeth. In orthopedic and dental surgery is applied for bone grafts or as a covering material for medical implants [81-84], in remineralization of enamel [85, 86] or to remove the heavy metals from wastewater [87]. In terms of implant coverage, it improves cell viability and adhesion, provides good rigidity and low elasticity. To mimic as accurately as possible, the chemical composition of the bone tissue, calcium from hydroxyapatite can be partially replaced with elements such as magnesium, silicon, zinc, strontium in small quantities. The resulting effects led to thermal stability, good solubility, and a favorable response in terms of bone regeneration [88-101].

The interaction between proactive compounds extracted from plants and hydroxyapatite is a new concept and is highlighted in figure 2. The literature studies show that medicine is progressing from one year to the next to find personalized treatments for everyone with medical conditions. In this context, it is desired that patients be treated targeted and less traumatizing as possible so that the beneficial effects are as fast as possible. Although the concept requires extensive daily study for continuous progress in the development of composite materials, the mechanism of action will be elucidated and ready for application.

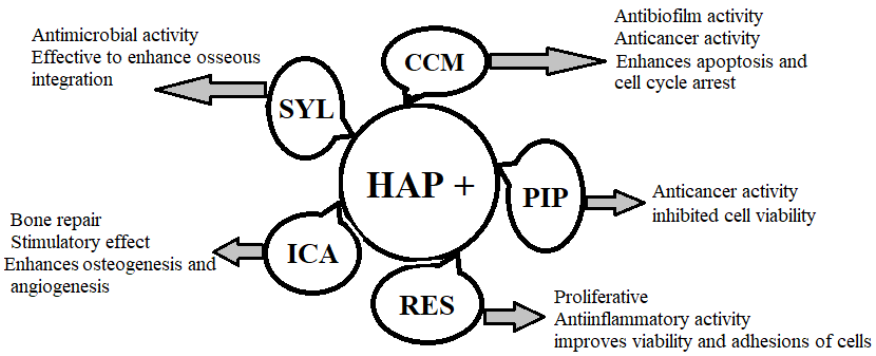

Fig. 2. Biomedical applications of the interactions between hydroxyapatite and bioactive compounds extracted from plants

Regarding the improvement of ***hydroxyapatite with silymarin***, the specialized literature shows that together they have antimicrobial activity against pathogens e.g. *Pseudomonas sp, Staphylococcus aureus, Streptococcus mutans, Enterococcus faecalis* and *Candida albicans* [102]. Silymarin is known to promote osteoblast proliferation, inhibits osteoclast proliferation and helps to bone regeneration. So, Z.-S. Tao and his group incorporated silymarin into hydroxyapatite and used it as a coating for titanium implants. They highlight that SIL promotes bone formation around the implant in osteoporotic rats; increases implant osseointegration and improves trabecular microarchitecture. The conclusion of this study is that SIL can be an effective approach to enhance osseous integration of the HAP coated implant in bone [103]. To improve the bioavailability of Silymarin, formulations were developed for oral administration, such as nanoemulsions, nanostructured lipid carrier, solid nanodispersions, inclusion complexation, polymeric and inorganic nanoparticles, liposomes, and solid lipid nanoparticles [104]. An idea that can open new research area is forsterite as an alternative carrier for silymarin which may allow controlled drug release at the target site [105-114]

Curcumin functionalized hydroxyapatite has anti-biofilm activity tested on human osteoblast-femural cell line (HO-f). W.-H. Lee et al highlight that after 3 days of incubation osteoblast proliferation was lowered. They also show that if incubation period is prolonged to two weeks no significant differences were observed. However, CCM functionalized HAP inhibits bacterial cell attachment and subsequent biofilm maturation stages in both S. aureus and P. Aeruginosa [115]. Another study conducted by Ş. M. Eskitoros-Togay tested CCM-HAP against breast cancer MCF7 cells line. They loaded CCM-HAP into poly (ε-caprolactone)/poly (ethylene oxide) and prepared 7 samples noted PCL/PEO, PCL/PEO/0.1wt.%HAP, PCL/PEO/0.3 wt. %HAP, PCL/PEO/0.5 wt. %HAP, PCL/PEO/0.1 wt. %HAP-CCM, PCL/PEO/0.3 wt. %HAP-CCM, PCL/PEO/0.5 wt. %HAP-CCM. The obtained results of viability of cells show after 24 h of incubation and 94 %, 92 %, and 93 % for PCL/PEO/0.1HAP, PCL/PEO/0.3HAP, and PCL/PEO/0.5HAP respectively. After 48 h incubation 93 %, 89 % and 90 %. In the case of PCL/PEO/0.1 wt. %HAP-CCM, PCL/PEO/0.3 wt. %HAP-CCM, PCL/PEO/0.5 wt. %HAP-CCM [116].

W.-H. Lee et al also study this kind of composite, CCM-HAP but the surface of HAP was functionalized with different carboxylic acids to harbor negative charges and increase drug (CCM-NPs) loading capacity of HAP. Their conclusion was that CCM loaded carboxylic acids-HAPs on MCF-7 cells were directly correlated to the release rate of CCM nanoparticles from HAP carrier, depending on the types of carboxylic acids used. This type of composite showed higher anti-

cancer activity and resulted in enhanced apoptosis and cell cycle arrest compared to unmodified HAP [117].

K. AbouAitah and his group prepared nanoformulations consisting in aggregates of ***HAPs loaded with PIP*** and tested in vitro against HCT116 cells (colon cancer), MCF7(human breast adenocarcinoma) and Caco2 (human colon carcinoma cells) and WI-38 (human fibroblasts cells. The obtained results show potential for targeting this kind of colon cancer cells, but a strong reduction was also shown on MCF7 cells when treated with HAP-PIP at pH 9.3, 200 µl incubated for 72h. Unloaded nanoparticles exhibited weak cytotoxicity towards WI-38 fibroblasts. They concluded that the cell viability of cancers depended on cell line, concentration, incubation time, and delivery method of PIP. Also, increasing the incubation time from 48 h to 72 h inhibited the cell viability of all investigated cells [118].

Resveratrol (RES) and hydroxyapatite (HAP) composite is known to have proliferative activity in the case of human adipose-derived mesenchymal stromal stem cells (hASCs). nHAP and RES improve the adhesion and spreading of cells, improve viability, metabolic activity, and mitochondrial potential. The composite has a great pharmacological potential as carrier for bioactive compound delivery [119]. In the case of RAW264.7 cells (leukemia cells in mouse macrophage cell line) the researchers synthesized nano-hydroxyapatite (n-HA)/resveratrol (Res)/chitosan (CS) microspheres. They obtained anti-inflammatory activity evidenced by the decreased expression of pro-inflammatory cytokines TNF-α, IL-1β and iNOS in RAW264.7 cells in a dose dependent manner. This kind of composite could stimulate BMSCs proliferation and osteo-differentiation, as well bone remodeling under osteoporotic condition [120].

Icariin loaded on micro/nano HAP granules was tested on rat femoral defect model on bone mesenchymal stem cells (BMSCs) at two concentrations 200 µM and 2000 µM. The conclusion of study was that icariin could promote the osteogenic differentiation and expression of angiogenic factors of BMSCs. At concentration of 200 µM, icariin had the strongest stimulatory effect but in 2000 µM could enhance both osteogenesis and angiogenesis in vivo. They evidence that a small molecule of icariin could penetrate HAP network that could slow down the release rate in the 2000 µM group [121]. Icariin was also loaded in chitosan/nano-sized hydroxyapatite (IC–CS/HA) by J. Fan et al. They study the bone repairing, more specify the bone marrow derived stroma cells (BMSCs). The loaded icariin in this composition demonstrates the stimulation of bone marrow derived stroma cell alkaline phosphatase activity and formation of mineralized nodules [122].

Regarding ***Carotenoids and hydroxyapatite,*** the literature presents the potential use of hydroxyapatite nanoparticles as adsorbent for β-carotene/lycopene. S. Kongsri et al demonstrate through adsorption isotherms that

the adsorption behaviours of the carotenoids on hydroxyapatite nanoparticles and chitosan substrates were well fitted [123]. They found that the adsorption capacity values for lycopene are greater than those of β-carotene for both hydroxyapatite nanoparticles and chitosan. They say that hydroxyapatuite can be a good substrate for carotenoids adsorption in physiological functions. In other study conducted also from S. Kongsri et al investigate the adsorption of carotenoid from tomato extract using nanocrystalline fish hydroxyapatite in the presence of sodium dodecyl sulfate. Adsorption interactions are possible through various mechanisms such as ion exchange, hydrophobic interaction and electrostatic forces. In this sense, the carotenoid can be adsorbed on fish hydroxyapatite surface through hydrophobic interactions [124].

This is how the incorporation of plant compounds into hydroxyapatite-based composites can bring about improvements in the treatment of various types of cancer cells or even in the case of bone regeneration. It is a broad idea that requires continuous development and intense application on the cells to obtain results with desired effects.

6. Silymarin and bioactive compounds interaction with carotenoid

Carotenoids are natural pigments that can protect the body against various diseases, enhance the immune system, and play a role in cell membrane stability, photosynthesis, and cellular differentiation. They also contribute to health benefits through anti-cancer, anti-inflammatory, anti-bacterial, anti-diabetic and neuroprotective activity [125-128]. Carotenoids are found in plants such as vegetables, fungi, algae, or bacterial species and can also prevent atherosclerosis, age-related macular degeneration, and other chronic diseases [129-131]. Two groups of carotenoids exist: xanthophylls (Canthaxanthin, Zeaxanthin, Lutein, Astaxanthin) [132-137] and carotenes (β-carotene, Lycopene) [138, 139] both having antioxidant properties.

Specialized literature shows that carotenoids films can be studied by Langmuir-Blodgett Technique. Some studies conducted by M. Tomoaia-Cotisel and coworkers produced self-assembled and supra-molecular structures at air/water, oil/water, benzene/water and gas/liquid interfaces [140-155]. This approach opened new potentials of research in monolayers and multilayers structures with biological and biomedical importance for life science. The interaction with various biomolecules such that mentioned in this review, may be explored by this technique that can simulate the cell membrane using a single layer oriented at air/water interfaces. The interest to develop new biomaterials for regenerative medicine, tissue engineering, cancer therapy, self-assembled scaffolds and drug delivery make from Langmuir Blodgett Technique (LBT) an essential instrumentation in manufacture of thin film in which the surface potential of biomolecules can be measured to characterize the miscibility. The

technique is useful to biomedical applications by nanoscale interactions. Such applications are based on self-assemblies of collagen [156-158], lipids, phospholipids and galactolipids [159-165], antioxidants [166-169], fatty acids [170-173], proteins [174, 175], cholesterol and lecithin [176-178], drugs [179-181].

The literature highlights study the orientation and localization of carotenoids in the lipid membrane. A schematic representation of carotenoids that are hydrophobic molecules can be seen in Figure 3.

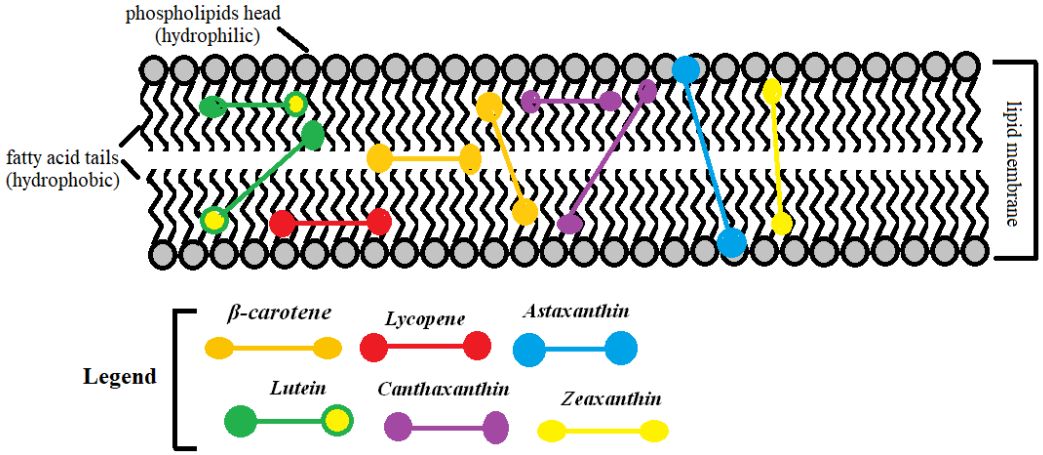

Fig. 3. Localization and orientation of carotenoids in lipid membrane

Carotenoids can incorporate into lipid membrane starting from the strongest to the weakest. C. Tan et al shows that liposomes can act as a delivery system for various carotenoids, so they can display different loading ability into lipid bilayer [182]. The macular carotenoid is oriented perpendicularly to the membrane surface which ensures high solubility and stability [183]. J. Widomska and collaborators highlighted that macular xanthophyll interact with proteins and lipid from membrane to absorb light energy, modulate oxidative stress and influence signal transduction cascades [184].

Lycopene ($C_{40}H_{56}$) is a carotenoid found abundant in tomato but also in small amounts in guava, pink grapefruit, papaya, and watermelon. Is a lipophilic red color pigment that derived from an acyclic structure with 13 carbon double bonds (11 conjugated double bonds and 2 non-conjugated double bonds) arranged in a linear array. It is insoluble in water and soluble in organic solvents. As can be seen in figure 3, lycopene is oriented parallel to cell membrane surface within the lipid bilayer, and it is expected to be poor hydrophilic antioxidant due to its limited interaction with aqueous phase radicals in the lipid bilayer [185].

The literature shown that lycopene can arouse the proliferation of osteoblast-like SaOS-2 cells (a human osteosarcoma cell line which displays

several osteoblastic features) and has inhibitory effect on MC3T3 cells proliferation; MC3T3 cell line is an osteoblast precursor cell line derived from mouse calvaria. Also, lycopene may be beneficial in cardiovascular diseases and ulcers; as an antioxidant, it can prevent the oxidative damage of DNA, lipids and proteins and induces apoptotic cell death. It seems that lycopene also decreased Bcl-2 and increased levels of Bax, inhibited phosphorylation of extracellular signal-regulated kinase, and it may protect against the development of gastric cancer [186-188].

The *β-carotene* is the most abundant carotenoid in the human body and derived from the acyclic structure, $C_{40}H_{56}$, possesses a long chain of conjugated double bonds and two β-iononic rings. The β-carotene and lycopene orientation in the lipid membrane, as seen in figure 3, can be governed by van der Waals interactions with the hydrocarbon acyl chains of lipid molecules, forming the hydrophobic core of the membrane [189]. Is found in most vegetables and fruits such as carrots, spinach, kale, parsley, summer squash, tomato's, sweet potatoes, broccoli, and mango. It has the highest bioactivity and acts as a precursor to produce vitamin A. β-Carotene can be partially converted to vitamin A, but the unconverted β-carotene is incorporated in chylomicrons, secreted into the lymph, and then transported to the liver. β-Carotene can reduce the risk of osteoporosis. As a mechanism in cancer prevention β-carotene acts as a pro-oxidant in leukemia cells (HL-60) and colon adenocarcinoma cells (LS-174 and WiDr). Also, in lung cancer/lung carcinoma cell (A549) increase the oxidative stress marker (8-oxo-dG). Inhibit cancer cell growth by increased production of ROS via activation of NF-κB in leukemia and colon cancer/human leukemic cells (HL-60), colon adenocarcinoma cells (LS-174 and WiDr) and activate apoptosis in Leukemia/HL-60 cells. In gastric cancer/AGS cells β-carotene increased levels of caspase 3, ROS, cytochrome c and Bax (proapoptotic effector molecules from Bcl-2 family) [190-193].

Lutein is a 40-carbon hydroxylated carotenoid with β and ε type ionone ring and acts as a pro-oxidant in breast cancer and increases the levels of phosphorylated p53 and heat shock protein 60 [190, 193-195]. Its orientation in cell membrane can be seen in figure 3. X. Gong et al, in their study highlighted that the treatment with lutein on MDA-MB-468 and MCF-7 cells inhibited cell cycle progression. An increased population of cells in G1 phase, a reduction in G2 phase in MDA-MB-468 cells, as well as a decreased cell population in G1 phase and an increase in G2 phase in MCF-7 cells was observed [196]. It can be found abundant in marigold flowers, broccoli, lettuce, cilantro, kale, and sweet potato but also in small amount in pepper, maize, black palm, and pumpkin [197].

Astaxanthin with molecular formula $C_{40}H_{52}O_4$ consists of two terminal rings joined by a polyene chain [198]. It has two asymmetric carbons located at the 3, 3′ positions of the β-ionone ring with hydroxyl group (-OH) on either end of

the molecule. The position in cell membrane can be seen in figure 3, the terminal ring is able to scavenge radicals at the surface and in the interior of phospholipids membrane. Its membrane insertion is due to its linear molecular appearance and extends across the entire width of the lipid membrane [199, 200]. It is a red pigment found naturally in shrimp, crab, and salmon, is insoluble in water but soluble in most organic solvents. It is a keto-carotenoid synthesized by plants and microorganisms [201]. In the case of cancer treatment, astaxanthin significantly inhibited prostate cancer DU145 cells proliferation and promotes the apoptosis of these cells.

In the literature is highlighted that astaxanthin effectively inhibits the cloning ability of DU145 cells, downregulates the gene expression of JAK2, BCL-2, NF-kB and upregulates the gene expression of BAX, Caspase3 and Caspase9 [202]. In the case of human glioblastoma cell line U251MG, astaxanthin suppressed cell viability at concentrations of more than 1 and 0.1 μM. It is shown that the treatment for 48 h decreased the expression of cyclinD1 and increased the expression of p27 [203].

Zeaxanthin is a yellow-orange xanthophyll also known as β,β-carotene-3,3′-diol which contain two hydroxyl groups with a higher polarity. The presence of the two hydroxyl groups determines its orientation in lipid membrane, figure 3, and enhances the stability of zeaxanthin [183]. It has been reported by literature to exhibit cytotoxic effects. It is a lipophilic compound insoluble in aqueous media. It can induce G2/M cell cycle and apoptosis in gastric cancer cells by up-regulating Bax pro-apoptotic factor and down-regulating Bcl-2 anti-apoptotic proteins. Zeaxanthin has been shown to have protective effects in eyes (prevents AMD and cataract), liver (reduce ROS and protect against nonalcoholic fatty liver disease), skin (inhibits sunburn) and arteries (protects against atherosclerosis) [204].

It was demonstrated by in vivo and in vitro results that zeaxanthin and lutein has protective effects against chronic eye and cardiovascular diseases, such as age-related macular degeneration (AMD), cataract, coronary heart disease, and stroke [205].

Canthaxanthin (β,β-carotene-4,4′-dione) with ($C_{40}H_{52}O_2$) is a red-orange xanthophyll's that has nine conjugated double-bonds terminated by two oxo substituents at positions 4 and 4′ of the β-ionone backbone. Its orientation in lipid membrane, figure 3, is roughly perpendicularly to the surface of the membrane but also can be oriented parallel to the membrane, localized in the headgroup region. Canthaxanthin can modify the properties of membrane such as promote extended conformation of alkyl lipid chains, can modify the surface of lipid membrane in gel state and promote the aggregation of lipid vesicles [206]. It is used in cosmetics as a natural tanning agent who produces an orange-brown colour to skin. In vivo results highlighted that canthaxanthin led to decrease in

lipid peroxidation by preventing liver DNA damage, enhancing the antioxidant defense in rat liver and increased the activity of alkaline phosphatase [207]. A study conducted by P. Palozza and coworkers, it is indicating that canthaxanthin was able to inhibit the growth of malignant human cell lines, such as WiDr colon adenocarcinoma and SK-MEL-2 melanoma. Also, it induces apoptosis of these cells at the highest dose at the longest time of exposure (48h) [208].

Silymarin and lycopene investigation was conducted by L Garavaglia and coworkers where this combination was administrating in periparturient dairy cows. This combination could be a feed supplement with hepatoprotective and antioxidant activity. The treated cows show a higher milk yield at the beginning of lactation than untreated animals. The synergy effect can contribute to mitigate the negative effects on metabolic adaptation to the lactation [209]. In vitro study demonstrates the protective effect of ***beta-carotene and silymarin*** on DNA damage induced by L-arginine in lymphocyte culture [210].

R. P. Assis et al, in their study revealed that carotenoids maintain the benefit provided by curcumin alone. The co-administration produces effects on the increase in superoxide dismutase activity. ***Curcumin and lycopene*** in the case of diabetic rats is more effective in reducing glycemia than carotenoid treatments alone; it also led to significant body weight gain and provides benefits against lipoperoxidation [211]. ***Curcumin and lutein*** are beneficial in treatment of fecal oocyst in chickens. Their combination enhanced cellular and humoral immunity [212].

B. M. Steiner et al, in their research tried to resolve the lutein strong hydrophobicity and poor chemical stability when it is introduced in many foods. In this sense, some nanoemulsions was prepared that contain Casein-dextran Maillard conjugates, ***resveratrol*** and GSO (grape seed oil). Casein-dextran improves the physical resistance of nanoemulsions while resveratrol and GSO decreased ***lutein*** degradation and are effective at improving their chemical stability [213].

A. Kawamura and his group study the effect of anabolic nutrient-rich foods on muscle adaptation induced by resistance training. So, they highlighted that the combined intake of ***astaxanthin, β-carotene, and resveratrol*** can accelerate protein anabolism in the skeletal muscle of mice. Also, they concluded that even in a small amount this kind of combination can promote protein synthesis during the muscle hypertrophic process after atrophy [214, 215].

In the case of piperine and icariin interactions with carotenoids, information is limited or none. This is an approach that needs special attention to understand the mechanism of action. Beneficial results from this type of combination will exist from the moment when experts in this field will publish their obtained experimental data.

Biodegradable material such as calcium sulfate hemihydrate and composites based on gypsum have been used as local drug delivery systems or as construction materials in the living and non-living world [216].
All the data from this section require more details but the literature is limited once again. It seems that interactions of phytochemicals need someone to research this area to find information with medical potential.

7. Conclusions

This review is focused on Silymarin interaction with phytochemicals extracted from plants and their interactions with each other and with hydroxyapatite and carotenoids. Their efficiency was demonstrated in various cancer cells lines such as MCF-7 (breast cancer), bladder carcinoma, hepatocellular carcinoma, colon cancer (HCT116) and against pathogens (S. aureus and P. Aeruginosa). Also is debated the Silymarin combination with chemotherapeutic drugs (doxorubicin, paclitaxel, and 5-fluorouracil) and metallic nanoparticles such as gold and silver.

Herbal therapy demonstrates multiple biological activities in the treatment of chronic diseases and cancer (the cruelest disease in the world that causes millions of deaths a year regardless of age). The presence of medicinal plants in the world has been studied since ancient times and through the mechanism of action that has been intensively studied lately, it has been possible to prevent and maintain the balance between health and death.

However, this approach requires the design and development of new strategies and innovative nanomaterials not only in the treatment of cancer but also in bone regeneration, tissue engineering and viruses that are constantly beginning to appear.

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Notations and/or **Abbreviations**

CCM – curcumin, SIL –Silymarin, PIP – piperine, RES – Resveratrol, ICA – Icariin, HAP – hydroxyapatite, GNPs – gold nanoparticles, SNPs – Silver nanoparticles, DOX – doxorubicin, PCT – paclitaxel, 5-FLU – 5-fluorouracil, LBT – Langmuir Blodgett Technique

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