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 REVIEW

# Bioactive Compounds from Plants Used as Therapeutic Agents in Biomedical Applications - A Literature Review-

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**Abstract.** This review proposes an extensive study of some bioactive compounds produced by plants (piperine - PIP, curcumin - CUC, resveratrol – RES, icariin - ICA) with beneficial effects on human health. In addition to these compounds, the need for natural pigments, carotenoids in the body's daily diet and implicitly in nano-science and medicine is also debated. This study points to complexes of proactive compounds as well as their interaction with other drugs (e.g., doxorubicin: DOX, 5-fluorouracil: 5-FLU, paclitaxel: PCT) and metal nanoparticles (such as: gold nanoparticles: GNP, AuNP, and silver nanoparticles: SNP, AgNP) with applications in cancer cell lines and bacterial investigation, as well as using viral and fungal strains. This study also opens new opportunities of multi-functional metallic nanoparticles, realized by self-assemblies through molecular recognition among bioactive compounds on GNP or SNP, for their biomedical applications that require continuous development in terms of infections and the need to treat cancer and other diseases.

**Keywords:** *plant extract, carotenoids, flavonoids, plant bioactive compounds, chemotherapeutic drugs, GNP, SNP, health effect*

## 1. Introduction

Today, humanity is going through a difficult period in terms of public health. The medical system is overwhelmed by the large number of hospitalizations due to diseases caused by viruses, bacteria, pollution and other factors responsible for the disease of the living being. Despite the efforts of researchers and practicing physicians, the progression of disease has increased rapidly with the emergence of mutations and replication of microorganisms. In this sense, the need to develop nanostructures based on biomolecules such as piperine, curcumin, resveratrol, icariin, doxorubicin, 5-fluorouracil and paclitaxel can significantly contribute to understanding and improving the mechanisms of action in treating various diseases and eradicating the factors that cause disease.

The functioning of biomolecules either individually, combined or in the absence / presence of metallic nanoparticles (GNP, SNP) would present a revolutionary method in the field of biomedical applications, opening opportunities for correct diagnosis and treatment of diseased tissues. Thus, research has been intensified to obtain innovative and intelligent synthetic nano-biomaterials that correspond to the composition of the tissues to be cured.

*Piperine* (PIP) is an alkaloid found in black pepper (*Piper nigrum*) which is used especially as a spice in food preparation. Studies in the literature have shown that piperine is very useful in the treatment of pain, flu, rheumatism, blood circulation, vascular cell modulation. It has also been explored for its biological activities such as anti-oxidant, anti-cancer, anti-microbial, anti-inflammatory, anti-fungal, anti-ageing, anti-allergic, anti-arthritis, anti-diabetic, anti-obesity, and for its potential therapeutics (such as, hepatoprotective, immunomodulatory, analgesic), as observed in table 1 [1-3]. Paying attention to the plant, *Piperum nigrum*, which Mother Nature gave to the living being, it was possible to extract piperine and enhance the quality of human life in different ways. Scientific research has succeeded in revealing the properties of this compound for pharmaceutical and biomedical applications. Continuing its study in different compositions with other nanostructures, such as ceramic, metallic, and polymeric biomaterials, opens new horizons of applicability. Such an approach would discern the mechanism of action of these innovative materials both applied individually and in composite materials.

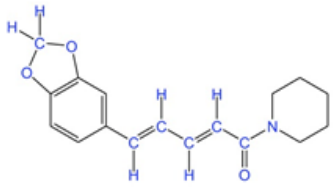
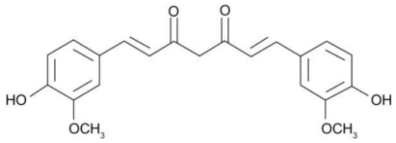
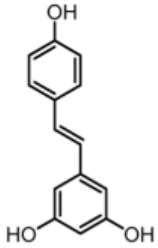
*Curcumin* (CUC) is a polyphenol compound isolated from *Curcuma Longa* rhizomes [4, 5]. It is a yellow compound used in the food industry as a spice. Currently it has managed to attract attention through its effects on human health, presented in table 1, such as anti-oxidant, anti-cancer, and analgesic, anti-inflammatory, anti-septic, anti-viral, anti-diabetic, anti-parasitic and protective ability on the liver. From this point of view, it has been used by Chinese and Indian medicine in the various treatment of illness [6, 7]. Currently, research has shown great interest in the development of curcumin-based drugs. Given its pharmacological activities, such an approach is essential in the production of composite nano-materials with biomedical applications that open new areas of research and facilitate the understanding of the mechanisms of action on tissues to be cured [8].

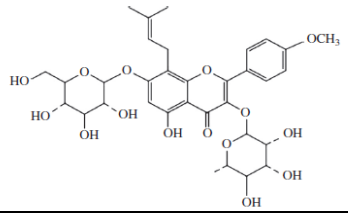
*Resveratrol* (RES) is another polyphenol found in more than 70 species of plants, nuts and fruits. Its use has been made since ancient times in ayurvedic medicine as a protector of the heart, neurons, lung, eyes, kidney, muscle and other organs. As science has advanced, resveratrol, a natural ingredient, has revealed a number of health-beneficial biological activities, table 1, such as anti-cancer, anti-diabetic, anti-viral, anti-microbial, anti-aging, anti-oxidant, anti-inflammatory, anti-fungal [9-11]. In this sense, it is considered a natural antibiotic that can

improve the quality of life. Literature has demonstrated its benefits on health. Also, studying resveratrol may conduct to other spectacular results by conjugation with drugs, metallic particles, and ceramic particles, encapsulated in polymeric matrix as a carrier. All kind of compositions are good if they can be applied to the sanitary system [12].

*Icariin (ICA)* is a natural flavonoid isolated from *Epimedium* family [13]. Icariin improves bone formation by stimulating osteogenic differentiation of bone marrow-derived mesenchymal stem cells and promoting the maturation of osteoblasts [14]. Research studies show that icariin exhibits a various range of biological activities such as anti-osteoporotic, anti-tumor, anti-inflammatory antioxidant, anti-depression, and potential therapeutic (neuro-protective and cardio-protective) that can be seen in table 1 [15-17]. *Icariin* is an important compound that fights against various illnesses.

Table 1. Biological activity and therapeutic potential of piperine, curcumin, resveratrol and icariin

| *No.* | *Compound and chemical structure* | *Biological activity* | *Therapeutic potential* | *Refs* |
|---|---|---|---|---|
| 1. | Piperine  | Anti-cancer, anti-microbial, anti-inflammatory, anti-obesity, anti-ageing, anti-diabetic, anti-arthritis, anti-allergic, anti-convulsant, analgesic | Neuro-protective; Hypoglycemic and hypolipidemic agent; Hepato-protective | [1], [18-20] |
| 2. | Curcumin  | Anti-oxidant, anti-cancer, analgesic, anti-inflammatory, antiseptic, anti-viral, anti-diabetic, anti-parasitic | Hepato-protective | [5], [6], [21] |
| 3. | Resveratrol  | Anti-cancer, anti-diabetic, anti-viral, anti-microbial, anti-ageing, anti-oxidant, anti-inflammatory | Neuro-protective Cardio-protective Intestino-protective Reno-protective Pulmono-protective Reproductive Organs Protective Ophthalmo-protective Musculo-protective Vesico-protectiv | [9], [11], [22] |

| | | | | |
|---|---|---|---|---|
| 4. | Icariin  | Anti-osteoporotic anti-atherosclerotic anti-oxidant, anti-inflammatory anti-proliferative, anti-thrombotic anti-cancer | Neuro-protective Cardio-protective | [15]-17] |

It is observed from the tabulated data that these biomolecules have common biological activities but in the following the type of diseases or pathogens treatable will be presented largely.

By this review we want to point out the importance of what Mother Nature gave us, as natural therapy by which the plants containing ingenious biomolecule can offer various treatments that can cure the illness. This is evidenced by literature studies, selected experimental research and promising results on the treatment and healing of diseases.

Through these natural remedies, new frontiers of research and implicitly of novel biomedical applications are opened. We must mention that currently the most common condition among the population is that one which does not take into account age is namely cancer. So the development of new composites made by these biomolecules and conjugated with drugs and metallic particles are the new revolutionary therapies in the treatment of severe illnesses.

## 2. Individual and combination therapy of piperine, curcumin, resveratrol and icariin

So far, we have seen the biological activities of the biomolecules and their therapeutic potential. We will further discuss the impact on the body in case of application. Table 2 highlights the effects of these individually applied biomolecules and their combination [23-59].

Table 2. The effect of biomolecules both applied individually or in combination, on the human body

| *No.* | *Compound* | *Effect on human body* | *Refs* |
|---|---|---|---|
| 1. | Piperine | - arrests of cell cycle and cancer growth,<br>- effects on angiogenesis and extracellular matrix (ECM) degradation,<br>- disturb the redox homeostasis in cancer<br>- inhibits cancer stem cells (CSCs)<br>- inhibit tumor growth by inducing cell apoptosis and cell cycle blockage.<br>- protect the glycoprotein levels in serum and tissues against B(a)p that induce lung carciogenesis.<br>- protects against pyroptosis in myocardial ischaemia /reperfusion injury | [23-28] |

| | | | |
|---|---|---|---|
| | | - regulate the pro-antiangiogenic homeostasis in the retina of mice with diabetes | |
| 2. | Resveratrol | - decrease cancer cell proliferation<br>- inhibiter tumor growth and metastasis of lung cancer<br>- induce cell cycle arrest and cell apoptosis;<br>- induce cytotoxicity<br>- inhibited the growth and proliferation of a variety of cancer cells<br>- enhanced the cerebrovascular function<br>- promote cell viability and proliferation<br>- modulated the formation of new vascular networks<br>- ameliorate the mitochondrial respiratory dysfunction<br>- inhibited viral replication as well modulate the host immune response<br>- inhibited viral nucleocapsid protein translation<br>- reduce virus-induced apoptosis<br>- increases the expression of ACE2 on the cell surface<br>- decrease the number of infected cells and reduced the intracellular RNA levels<br>- decreased viral gene expression and viral protein synthesis | [29-34] |
| 3. | Curcumin | - protect renal cells and neural glial cells from oxidative stress<br>- enhance the activities of other anti-oxidants<br>- exhibits potent effects against cervical cancer<br>- enhanced the expression of p53 molecules in tumour cells<br>- suppress inflammatory cytokines (IL-6, IL-8), TNFα and IKKβ kinase in the saliva of patients<br>- causes the down-regulation of NF-κB, COX-2 and phosphorylated STAT3 in peripheral blood mononuclear cells<br>- reduced the total cholesterol and lowdensity lipoprotein cholesterol levels<br>- reduce the myocardial infarction<br>- increase the vascular endothelial function in postmenopausal women<br>- role in the pathogenesis of psoriazis, allergy, asthma, diabetes, obesity, neurogenerative disease | [35-38] |
| 4. | Icariin | - increases the secretion of extracellular matrix proteins<br>- enhances articular cartilage repair<br>- protects chondrocytes from lipopolysaccharide<br>- induce osteoblast proliferation, differentiation, and mineralization | [39-41] |
| 5. | PIP + RES | - enhances the bio efficacy of resveratrol with regard to cerebral blood flow effects<br>- effect on depressive-like behaviors<br>- enhance the radio sensitivity of cancer cell lines by increasing ROS generation<br>- co-crystallization improve the solubility of resveratrol | [42-48] |

| | | | |
|---|---|---|---|
| 6. | PIP + CUC | - could play a role in the treatment of COVID-19 by adjuvant therapy<br>- develop systemic therapy for leukemia<br>- Anti-malarial treatment of COVID-19<br>- Anti-proliferative potential in drug resistant human leukemia<br>- nano-carrier system in cancer therapy on HCT116 CRC cell line. | [49-53] |
| 7. | CUC + RES | - inhibiting of Aβ aggregation,<br>- reduction of oxidative stress,<br>- promotion of cell growth,<br>- inhibiting of cholinesterase activity,<br>- inhibiting of brain pro-inflammatory responses,<br>- prevention of neuronal cell death,<br>- caused apoptosis in cigarette smoke condensate transformed breast cancer epithelial cells<br>- inhibited apoptosis and prevent the activation of caspase | [54-58] |
| 8. | PIP + CUC + RES | - cytotoxic effects in MCF-7 cells<br>- decrease GLO1 activity and mitochondrial dysfunction. | [59] |

The data from the literature summarized in Table 2 highlight a wide range of effects of the four biomolecules obtained from plants. It is also observed that by combining them the potential of applications in medicine increases but they still require studies to understand the mode of action and the synergistic effect.

M. Zadorozhna and colleagues showed in their in vitro study on colon cancer that *piperine* is able to stop the cell cycle in the G1 phase, regulating cyclin D1 and D2 and their partners CKD4 and CDK6. It also increased the level of ROS in the HeLa cervical tumor and MCF-7 breast cancer line by stopping the cell cycle in the G2 / M phase. In the case of breast cancer, the more specific is the cell line MDA-MB-231 [23]. M. Zakariyyah Aumeeruddy et al.. showed that piperine decreases the expression of the protein associated with G1 and G2 by increasing the expression of p21 WAF1 / Cip1. It also inhibits the in vitro growth of triple negative breast cancer (TNBC) cells and inhibits the activation of Akt which has the role of survival in these cells [24]. L.-H. LAI shows in the case of the 4T1 cell line - a model of murine breast cancer, piperine can suppress and inhibit tumor growth by inducing apoptosis and blocking the cell cycle [26].

Piperine has a wide range of activities as shown in Table 1. Research by the group led by X. Guo has shown in experiments in rats that piperine can ameliorate and protect MIRI (myocardial ischaemia / reperfusion injury) from pyroptosis through the miR-383 pathway [25]. Another study indicates the importance of piperine against pulmonary carcinogenesis induced by B(a)p (benzo(a)pyrene) in mice. Piperine can modulate the level of protein-related carbohydrates being one of the signs of tumor genesis [27]. Recently, piperine has been shown to protect the retina of diabetic mice by regulating pro-antiangiogenic homeostasis [28].

All these studies highlight the effectiveness of piperine on the body both in vivo and in vitro studies. Its benefits are not fully elucidated, which opens new horizons for research and development of treatments among various diseases.

*Resveratrol* effects on human body are various but the cancer treatment remains in top. It seems that studies on the treatment of cancer have shown that RES inhibits the proliferation of cancer cells and induces cell cycle arrest and thus apoptosis. M. Yousef and his research team, through their study, treated A549 and H460 lung cancer cells with resveratrol. The results showed that RES inhibits growth and induces apoptosis and stops the G1 cell cycle [29]. Other studies seem to show that resveratrol is a good option in the treatment of bone and spine cancer. It prevents and alleviates pain by inhibiting glial activation and regulating the CX3CR1 gene. It induces apoptosis and inhibits cyclooxygenase in the spinal cord [30].

Clinical studies show that RES is a polyphenol with low cytotoxicity and protective effects against diseases. Given this aspect in pandemic times, it seems that RES has great potential on many viruses responsible for respiratory infections. S. Filardo et al., S. Pasquereau et al. and B. M. ter Ellen et al. demonstrated the anti-viral activity of RES on SARS-CoV-2. Both RES and its analogues inhibit viral replication and modulate the host's immune response [31-34]. So here, it is another natural compound, resveratrol, with multiple health benefits. Of course, the mechanisms of its action are not yet fully studied and are not yet fully elucidated. For this reason, the continuation of experimental research is essential in the development of new materials with biomedical applications and implicitly new potential therapeutic effects.

Another biomolecule with low toxicity and clinical evidence that indicates multiple health benefits is *curcumin*. It treats a wide range of chronic, inflammatory, metabolic, neurological, infectious diseases and last but not least cancer. B. Kocaadam & N. Şanlier support the hypothesis that curcumin is effective in the developmental stages of cancer by suppressing tumor invasion. A review by M. Wang et al. highlights the importance of curcumin in treating cancer, inhibiting cell proliferation in lung cancer and stopping the growth of colon cancer and medulloblastoma [35-38].

M.-L. Pérez-Lozano highlighted in their study in vitro and in vivo that *icariin* can increases the secretion of collagen type II and the expression of SOX-9 from extracellular matrix (ECM). It was observed diminish of MMP-1, 3, 9, 13, COX-2 and iNOs suppression by suppressing NF-kB signaling that induce the apoptosis [39]. L. Song and his group reported that icariin prevent bone loss, promote MC3T3-E1 osteoblastic cell proliferation, mineral content and reduce cell apoptosis. It also enhanced MC3T3-E1 cell differentiation and mineralization by increased the expression of differentiation markers, alkaline phosphatase (ALP) and collagen type I [40, 41].

*Piperine together with resveratrol* were studied by E. L. Wightman et al. and therefore showed that piperine improves the bio effectiveness of resveratrol and together they increased cerebral blood flow without altering its proper functioning [42]. Piperine has also been shown to potentiate the antidepressant effect of trans-resveratrol. This type of treatment has high potential and low side effects [43]. Regarding carcinogenic activity, RES and Pip have been shown to increase the radio sensitivity of tumor cells by generating reactive oxygen species (ROS). A report from BMB showed through their research on colon carcinoma CT26 and B16F10 cells that exposure to γ-radiation cause's apoptosis [44]. The results of studies in the literature have shown that piperine is significantly more important in terms of immunomodulatory and anti-inflammatory activity with respect to resveratrol, which is why it is suggested to pay special attention to it [45].

*Co-crystallization* is an alternative for active pharmaceutical ingredients. Co-crystallization means the formation of a system composed by two or more molecules at a certain stoichiometric ratio and maintained by hydrogen bonds. Through this the molecules incorporate each other forming new composition with same crystal lattice and new physico-chemical properties such as bioavailability, density, dissolution rate and other [46]. H. He and his group were involved in this new approach and it seems that they obtained different (four) crystals by crystallization of RES and PIP in molar ratio 1:2 dissolved in acetone and acetonitrile (1:1) and molar ratio 1:3 dissolved in ethyl acetate and toluene (1:1) through evaporation of solution under low temperature. It is known that piperine has three crystal forms (I, II and III) and the most stable is form I. The co-crystallization is produced through oxygen atom of the ketone of piperine that acts as a hydrogen bond acceptor forming hydrogen bonds with water and hydroxyl group of resveratrol. By co-crystallization, it was desired to improve the solubility of resveratrol [47, 48].

Given the difficult times of today when the SARS-CoV-2 virus has taken over the entire planet, increasing the mortality rate, a possible therapy that would significantly reduce the symptoms caused by the new virus, the need for oxygen, remdesivir injections and thromboembolic effects, would be that of *curcumin with piperine*. This result was demonstrated by the study conducted by K. S. Pawar and his collaborators in which he also specified that this treatment would reduce the increased mortality rate and treatment costs [49]. Another recent study on the combination of curcumin with piperine is that it is a possible anti-malarial drug. This research was based on strong antioxidant effects of individually applied curcumin and piperine causing damage to the parasites' DNA. Their combination is thought to limit the development of parasites but requires extensive studies to understand the mechanism of action on this therapy [50]. N. Li et al. investigated the application of the two molecules together in the case of human HL60

leukemic cells. They demonstrated through the obtained results the inhibition of HL60 cell growth showing a maximum inhibitory concentration (IC50) of 25 and 30 μm. Induction of mitochondrial apoptosis has been observed and therefore HL60 leukemia cell migration has been suppressed [51]. In colorectal cancer, HCT116 cells were used to test the potential of curcumin with piperine. Piperine is known to improve the therapeutic effect of curcumin and cell viability has reached 20% after 72 hours [52].

Regarding their ***co-crystallization***, the literature highlights only a patent of S. Chava and coworkers in which they obtain co-crystals that include ***curcumin and piperazine*** in a molar ratio of (1:1) and (2:1). Piperazine is a part of the structure of piperine. The piperazine was dissolved initially in acetonitrile at room temperature and then added the curcumin. After 6 hours the material was filtered and analyzed. They obtained co-crystal in form I of CUC-Piperazine (1:1). For molar ratio (2:1) piperazine was dissolved in methanol at room temperature, then added curcumin and after 4 hours the material was filtered, dried at room temperature and analyzed [53].

The *combination* of polyphenols *curcumin* and *resveratrol* is another cancer treatment strategy acting against proliferation, metastasis and cell death. These two components have strong antioxidant activities that could prevent neurodegenerative diseases such as Alzheimer's. In this sense, it inhibits Aβ aggregation and brain proinflammatory responses, reduces oxidative stress, prevents the death of neuronal cells and improves neuro-protective activity [54, 55]. Anti-proliferative effects in the colon and hepatocellular carcinoma were highlighted by A, Shindikar et al. They also showed that it can cause apoptosis in the epithelial cells of breast cancer, but more studies are needed to elucidate the mechanism of action. The synergy produced inhibits the IKK and the proteasome by blocking the genetic expression regulated by NF-kB and NF-kB [56, 57].

***Co-crystallization*** of these proactive compounds was possible using supercritical solvent technique to improve the components solubility and dissolution rate. It seems to be the single study of obtained RES-CUC co-crystal up to now. Supercritical solvent technique uses the effects of a mixture of solvents and supercritical fluids like $CO_2$. CUC and RES in molar ratio 1:1 were used and fluid mixture $CO_2$ and acetone. There was added in co-crystallization chamber setting the parameters like pressure 9.0 MPa and time 60 min. When atmospheric pressure is reached the *co-crystallization chamber* was depressurized and then the solids collected. By this technique the *RES-CUC co-crystal* was successfully obtained. The results obtained from experiments show that it can be used as anti-inflammatory, antioxidant and anti-nociceptive agent [58].

At last, the combination of the three molecules, *piperine, curcumin* and *resveratrol*, demonstrates in a research conducted by B. Schmidt, the cytotoxic

effects in MCF-7 cells and decreases mitochondrial membrane potential by increasing ROS level or mitochondrial protein glycation [59].

Piperine, curcumin, resveratrol and icariin are natural medicines effective in the treatment of various types of cancer, neurodegenerative disorders (Alzheimer, Parkinson, Sclerosis) and other illness. Cancer is a condition in which malignant cells multiply uncontrollably and invade healthy tissues. This condition is a major cause of death in the world, which is why the literature debates this topic very intensely. The neurodegenerative disorders can cause disruption of function and structure of neurons, and they also affect the movement, cognition, memory and disability.

So, the nature and nanotechnology give us all the support to improve the monitoring, diagnosis and treatment of various disorders [60].

## 3. Combination of piperine, curcumin, resveratrol and icariin with drugs

Drug resistance is a major threat to public health as it leads to difficult situations in terms of treating various conditions such as cancer or bacterial and viral infections. Combating these conditions has become difficult due to the improper and abusive use of drugs, for which the effectiveness of their individual application decreases. The current need to develop new treatments has led to the design of powerful remedies based on drugs functionalized with plant extracts.

The present review aims to highlights the interactions of PIP, CUC, RES and ICA with drugs such as doxorubicin (DOX), 5-fluorouracil (5-FLU) and paclitaxel (PCT) from specialized literature.

*Doxorubicin* (*DOX*) is a chemotherapeutic drug used intensively against various types of cancer tumors. It is known under the anthracycline name, an antibiotic that if it is used in large doses can produce damage on heart tissue. It is used due to its ability to inhibit the topoisomerase II leading changes in chromatin structure and generate ROS to damage biomolecules [61, 62].

*5-Fluorouracil (5-FLU)* is an antimetabolite drug used also to treat different types of cancer. When it is administered alone, the cytotoxic effect is induced through inhibited cellular thymidylate synthase [63, 64]. Studies in the literature show that anticancer drugs allow the addition of additional compounds which alter the morphology and function of proteins. Their incorporation into various assemblies designs nanostructured materials for medical applications [65-67].

*Paclitaxel (PCT)* is an antimitotic drug known as *taxane*. It is the most used as chemotherapy agents in early stage and metastatic breast cancer, ovarian germ cell tumor, cervical, nasopharyngeal and non-small cell lung cancer. His efficiency in the cancer therapy is given by concentration dependent effect like all drugs and causes mitotic arrest [62, 68, 69].

By this approach new strategies are open up for solving unresolved issues. Also, the formed complexes could manifest protective and healing properties of the afflicted tissues. The biggest goal of all researchers is to find a cure leading to cancer eradication. So, in table 3 are shown the effect of complex's formed by plant extract and cancer drugs on human body [70-97].

Table 3. Effect of formed complexes on human body

| *No.* | *Complex* | *Effect on body* | *Refs* |
|---|---|---|---|
| 1. | CUC+DOX | - Curcumin potentiates the antitumor activity of DOX<br>- curcumin up-regulates expression of Bax, caspase-9, p53 and p21<br>- induces apoptosis in cancer cells<br>- capable of ameliorating DOX toxicity | [70], [71] |
| 2. | RES+DOX | - inhibits the inflammatory response (NF-kB, COX-2)<br>- induces apoptosis and autophagy in breast cancer<br>- inhibiter biological functions of MCF-7/DOX cells<br>- promotes cell apoptosis in vitro<br>- imped tumor growth in vivo<br>- cytotoxic effects in HeLa and Caski cells and apoptosis | [72-75] |
| 3. | PIP+DOX | - Piperine inhibits the efflux of anticancer drugs (doxorubicin and mitoxantrone) enhancing their cytotoxicity in a dose dependent manner.<br>- enhanced the cytotoxicity of doxorubicin in Caco-2 and CEM/ADR 5000 cells.<br>- Piperine alleviates doxorubicin-induced cardiotoxicity via activating PPAR-γ in mice<br>- Piperine blocks the accumulation of DOX-induced inflammation<br>- Piperine inhibits cardiomyocytes apoptosis in response to DOX<br>- Piperine attenuates cardiac damage caused by doxorubicin | [76-79] |
| 4. | ICA+DOX | - Icariin enhances DOX-induced apoptosis<br>- icariin reverses the multidrug resistance induced by doxorubicin | [80, 81] |
| 5. | CUC+5-FLU | - Effects on various type of cancers<br>- induce apoptosis in nasopharyngeal cancer<br>- inhibited the growth of human gastric | [82-84] |

| | | | |
|---|---|---|---|
| | | cancer<br>- reduce toxicity induced by 5-FU in the treatment of Esophageal squamous cell carcinoma<br>- inhibited cell proliferation | |
| 6. | RES+5-FLU | - inhibition of cell growth and the induction of apoptosis in cancer cells<br>- regressed the oral squamous cell carcinoma to mild dysplasia<br>- enhance normal histological appearance of colon tissue | [85-87] |
| 7. | PIP+5-FLU | - increased 5-FU cytotoxicity in HL-60 and MDA-MB435 cells | [88] |
| 8. | ICA+5-FLU | - icariin potentiate the anti-tumor activity of 5-FU | [89] |
| 9. | CUC+PCT | - synergistic anticancer effect against human ovarian cancer cells<br>- blocked cell cycle arrest<br>- exhibits anti-proliferative effect<br>- induces apoptosis towards human breast cancer cells MCF-7.<br>- induced apoptotic cell death | [90], [91] |
| 10. | RES+PCT | - RES decrease the dose of paclitaxel needed without changing the efficacy of treatment<br>- RES sensitize paclitaxel-resistant cancers<br>- produce mitochondrial ROS and apoptosis | [92-95] |
| 11. | PIP+PCT | - synergistic interactions on MCF-7 breast cancer cell line | [96] |
| 12. | ICA+PCT | - icariin alleviated paclitaxel-induced neuropathic pain | [97] |

M. Ashrafizadeh et al. show in their study that *curcumin* administrated with *doxorubicin* decreased viability and proliferation of neuroblastoma cells. Also induce apoptosis via Bcl-2 down-regulation, Bax, caspase-9, p53 and p21 up-regulation. Curcumin enhances the accumulation of DOX in breast cancer cells and suppress chemo resistance [70]. M. Mohajeri et al. highlight that curcumin is capable to ameliorate DOX cytotoxicity by mechanism of actions such as antioxidant effects, ROS generation, NF-kB activity, Akt dependent induction of apoptosis, prevention of mitochondrial damage [71].

*Combination of resveratrol* and *doxorubicin* was shown in the research of G. Rai, to produce a synergic effect on the breast cancer cells MCF-7 and MDA-MB-231. They evaluate the synergy effect by means of the cumulative index (IC) and found that IC 20 of DOX and IC30 of RES was optimum. The beneficial effects of this combination of drugs enhanced DNA fragmentation and chromatin condensation also reduced wound healing time and clonogenic efficiency of breast cancer cells. Their optimum values were modulating the expression of genes and

cause the decrease of transcript level of NF-kB and COX-2 [72]. Z. Ma et al. had shown that the traditional Chinese medicine by rational combining of drugs produces synergy effect and reduces the adverse reactions. DOX and RES lead to less toxicity, good drug-release profiles and distribution in tumor tissue [73]. J.-M. Chen by their study highlight that RES + DOX had the strongest inhibitory effect on the cellular migration ability in the MCF-7 cell line promoting cell apoptosis rate in vitro and inhibiting tumor proliferation in vivo [74]. Another study conducted by Gh. Tomoaia et al. shows for the first time on human cervical cancer HeLa and CaSki cell line that DOX + RES mixture produces cytotoxic effect. Also they show that RES has a mild response in CaSki cells but when is mixed with DOX the response is more intensified [75].

In the case of *Piperine* and *Doxorubicin*, S. Li and his group have demonstrated that PIP potentiated the anticancer drugs such as DOX and mitoxantrone mediated by breast cancer resistance protein, multidrug resistance protein 1 and P-glycoprotein (P-gp). The concurrent administration of PIP and DOX changes the pharmacokinetics of DOX and modulates the P-gp [76, 77]. H. Li says in his study that piperine induces chemo sensitizing activity on doxorubicin by decrease of the cumulative index (IC50) value [78]. J. Yan and the group also found that piperine alleviated doxorubicin that induces cardiac injury, reduces myocardial oxidative stress, inflammation and apoptosis [79]. DOX is not the only chemotherapeutic agent that fights against cancer illness, but 5-fluorouracil is another candidate that needs to be tested in combination with plants biomolecules.

Multidrug resistance (MDR) is a major obstacle in the treatment of cancer. In this sense Z. Wang and his research group consider an alternative of combating this problem by combining *icariin with doxorubicin*. Through their studies they show that icariin reverses the multidrug resistance induced by doxorubicin and enhance**s** DOX-induced apoptosis. They examined the effect of icariin in the human osteosarcoma doxorubicin (DOX)-resistant cell line MG-63/DOX. It also increases the Rh123 accumulation and decrease in Rh123 efflux in MG-63/DOX cells by blocking the activity of MDR1 [80, 81].

Combining *curcumin with 5-fluorouracil* produces synergy effect on human colon cancer HT-29 cells by reducing the COX-2 expression, induces cell apoptosis and enhances the proliferation inhibition. Curcumin can potentiate the chemo-sensitivity of 5-FLU resistant colon cancer by down regulation of NF-kB activation. In the case of breast and nasopharyngeal cancer, curcumin reduces the toxicity induced by 5-FLU. In esophageal squamous cell carcinoma, curcumin induce**s** apoptosis and potentiates the antitumor effect of 5-FLU by inhibiting the NF-kB signaling pathways [82, 84]. The synergy effect is highlighted in study conducted by J. Y. Koo and collaborators on human gastric carcinoma (AGS

cells) where curcumin increased growth inhibition by blocking the G2/M transition [83].

*Resveratrol and 5-fluorouracil* is another drugs combination that can produce synergy effect. J. Dun et al., by studying this combination show that it produces tumor regression in the case of mouse skin carcinogenesis. Also RES can increase the number of S phase cells that is a reason why the produced synergy effect increased the percentage of apoptotic cells, activated the level of caspase-3, cleaved PARP and p53 protein and finally increased the Bax/Bcl-2 ratio [85]. The synergy effect on the oral squamous cell carcinoma and the combined therapy had regressed this affection to mild dysplasia [86]. In colon cancer the combination showed attenuation of injury severity. Res diminishes the cytotoxic effect of 5-FLU and enhances the normal histological appearance of colon tissue [87].

Regarding the combination of *piperine and 5-fluorouracil*, there are few literature studies. D. P. Bezerra has examined the interaction of piperine, piplartine and 5-fluorouracil in vivo and in vitro. The experimental results show that they lead to a semnificativelly increase in tumor inhibition. Piplartine increases the efficacy of 5-FLU in all tested cell line (SF295 -central nervous system, HCT-8 -colon human cell lines, HL-60 -leukemia and MDA-MB435 - breast), but on the other hand piperine increases the cytotoxicity of 5-FLU only in HL-60 (leukemia) and MDA-MB435 (breast) cells. They conclude that piplartine can increase the antitumor activity of chemotherapeutic drugs and decrease the side effects [88].

*Icariin combined with 5-Fluorouracil* is a potential treatment for colorectal cancer but is not enough studied and the mechanism of action is not very well understood. D.-B. Shi et al. investigated this combination on human colorectal carcinoma cell lines HT29 and HCT116 and showed that it dramatically reduced viable cells. Also showed that icariin suppressed tumor growth and enhanced the antitumor activity of 5-FU by inhibiting the NF-kB activity [89].

Antimitotic drugs such as *paclitaxel (PCT) and curcumin* show a promising treatment for cervical cancer. In the ovarian cancer they blocked cell cycle arrest at G2/M [90]. Y. Zhan and his research group highlighted that paclitaxel with curcumin exhibited synergistic growth inhibition and induced significant apoptosis in MCF-7 cell lines [91].

*Resveratrol and Paclitaxel* anti-tumor effects in Traditional Chinese Medicine, had shown in several studies that RES enhances the anticancer effect of PCT on liver cancer HepG2 cells and non-small cell lung cancer (NSCLC). Also, RES augments the effect of PCT in MDA-MB-231 breast cancer cells. It can be seen by studying the specialized literature that RES has synergy effect on PCT induced apoptosis [73, 92-95].

*Piperine combined with paclitaxel* is not very well studied. However, a study from M. N. Motiwala and V. D. Rangari found that PIP exhibits synergic effect with PCT on human breast cancer cell line MCF-7 [96].

*Icariin and paclitaxel* combination: specialized literature shows that icariin suppressed paclitaxel-induced neuro-inflammation. A study by Y. Gui et al., highlighted the effect of icariin on paclitaxel-induced neuro-inflammation and peripheral neuropathy in rats [97].

Scientific research on the interactions between biomolecules extracted from plants and drugs has been published in powerful journals revealed their impact on the treatment of various cancers. Important results have been highlighted and conclusions have been drawn regarding the potential effects on the living organism. It should be borne in mind that this alternative of combining plant extracts and medicines can open new biomedical applications for the treatment of other types of diseases.

## 4. Combination of piperine, curcumin, resveratrol and icariin with metallic particles (GNPs and SNPs)

Metal nanoparticles, NPs, such as silver (SNPs) and gold (GNPs) are well known in the scientific world due to their biological activities (anti-cancer, anti-microbial, anti-fungal, anti-inflammatory, anti-viral) and unique properties for monitoring the delivery of therapeutic agents to places that they want to be treated [98-117]. These NPs in combination with plant-derived biomolecules such as piperine, curcumin, resveratrol and icariin but also with other drugs such as doxorubicin, 5-fluorouracil and paclitaxel give rise to a new scientific field of research that could prevent and protect against side effects of anti-cancer drugs. Experimental research has shown the importance of using these gold and silver nanoparticles in medicine, especially in fighting bacterial infections where the medical system can no longer cope. Also, due to the improper use of drugs, there was the effect of resistance of pathogens to their application. The need to develop new methods to eradicate bacterial and viral infections and to treat conditions such as cancer is absolutely necessary. Such a revolutionary approach requires time for the accumulation of information, animal experiments that would significantly contribute to the elucidation of mechanisms of action and ultimately the effective application on human diseases. So, in table 4 is shows the information from literature the biological activity and application on cells [118-128].

Table 4. The use of metal NPs in different complexes that fight against cancer cells.

| *No.* | *Complexs* | *Biological activity* | *Cell line application* | *Refs.* |
|---|---|---|---|---|
| 1. | CUC+GNP | Anti-tumor<br>Anti-proliferative<br>Anti-oxidant | - Human colon cancer cells (HCT-116 cell line) and breast cancer cells (MCF-7 cell line)<br>- (NIH 3T3) embryo fibroblast cell line | [118-120] |
| 2. | CUC+SNP | Anti-cancer<br>immunomodulatory<br>and antiviral | - MDA-MB-435 and A-549 cells<br>- ACH-2 cells | [121],<br>[122] |
| 3. | RES+GNP | Anti-cancer<br>Anti-bacterial | - Breast (MDAMB-231), pancreatic (PANC-1) and prostate (PC-3) cancer cells<br>- A549 cell line derived from human lung Carcinoma<br>- MRC-5 derived from normal human lung tissue<br>- *Streptococcus pneumoniae* | [123-125] |
| 4. | RES+SNP | Anti-bacterial<br>Anti-tumor | - human breast cancer MCF-7 cells | [125]<br>[126] |
| 5. | PIP+GNP | neuroprotective | - | [127] |
| 6. | PIP+SNP | Anti-bacterial | - *Staphylococcus aureus*<br>- *Escherichia coli*<br>- HepG2 cells | [128] |
| 7. | ICA+GNP | - | - | - |
| 8. | ICA+SNP | Anti-bacterial | - | - |

Regarding the cytoxicity of *GNP functionalized with CUC* a research conducted by N. S. Elbialy et al. on HCT-116 and MCF-7 cells shows that a concentration 0.72 μg $mL^{-1}$ decreases the viability and produces morphological change [118]. P. Khandelwal et al. have prepared gold quantum clusters and gold nanoparticles conjugated with curcumin. They show the *in vitro* cytotoxicity on (NIH 3T3) and (MCF-7) cell lines. In the case of MCF7 cells treated with curcumin gold quantum cluster it was inhibited the growth inducing the apoptotic process and finally cells death. The curcumin functionalized gold nanoparticles are less efficient than curcumin conjugated gold quantum clusters [119]. On the other hand, S. Nambiar and collaborators show that curcumin functionalized gold nanoparticles present cytotoxicity in human prostate cancer cells (PC3) by decreasing the serum protein. Also they present antioxidant activity [120]. The literature researches contribute through experimental results to the completion of biomedical applications. So, curcumin encapsulated in silver nanoparticles was shown by S. Garg and A. Garg, to be important in tumoral cells (MDA-MB-435 and A-549 cells); there is a dose dependent effect on the capacity of releasing the

curcumin in 12h. This formulation presented an inhibiting effect on cell growth and decreases their viability when the concentration of curcumin is increased [121]. *Curcumin and SNP* have demonstrated their antiretroviral effects in the ACH-2 cells latently infected with human immunodeficiency virus (HIV)-1. R. K. Sharma et al. conclude that curcumin and SNP reduce replication of HIV by inhibited NF-kB translocation and downstream expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α [122].

Another important complex is *RES + GNP* used in anticancer and antibacterial activity. V. C. Thipe shows the resveratrol corona effect on GNP. The efficacy of RES-GNP was evaluated against breast, pancreatic and prostate cancer cells (MDAMB-231, PANC-1 and PC-3). They demonstrate the synergy effect by entry of RES-GNP into tumor cell and the anti-angiogenesis properties of GNP [123]. In the study conducted by C. Ganesh Kumar et al. RES conjugate GNP and cell viability was assessed against A549 (human lung carcinoma) and MRC-5 (human lung tissue) cell line. The results show a significant reduction (50%) in the viability of A549 cells but in the case of MRC-5 cell they did not exhibit any cytotoxicity [124]. S. Park et al. highlighted the antibacterial activity on Gram positive and Gram negative bacteria. They use in the study 22 strains. The RES-GNP is stable and most effective against *S. pneumoniae* infections [125].

*RES+SNP* also were reported that have antibacterial and anticancer activity. In the case of MCF-7 cell this combination shows growth inhibition. In conclusion, RES+SNP reflect synergy effect against tumoral cells [125, 126].

In the case of piperine combined with metallic nanoparticles, studies are less. So, *PIP+GNP* it was reported that alleviate neurotoxicity. One such study was conducted by S. Srivastav and his group using Drosophila melanogaster, a species of dipteran known as vinegar fly, as a model [127]. In the case of *SNP and piperine* M. Prabakaran et al. show the antibacterial activity against *E. Coli* and *S. Aureus* that was effective in inhibiting the growth. Also they tested this combination on HepG2 cells but the concentration was to low so the damage of cell was impossible [128].

## 5. Combination of cancer drugs with metallic particles (GNP and SNP)

Another important use of chemotherapeutic drugs is the combination with metallic nanoparticles, which may include the fight against cancer cells; see details in table 5 [129-140]. This kind of combination is promising for the treatment of cancer.

Table 5. The use of chemotherapeutics drugs in combination with GNP and SNP

| *No.* | *Complex* | *Effects/activity* | *Cell line application* | *Refs.* |
|---|---|---|---|---|
| 1. | DOX + SNP | Anti-proliferative<br>Anti-cancer | T47D<br>MCF7<br>H9c2 | [129],<br>[130] |
| 2. | DOX+GNP | Cancer therapy | 4T1 (mouse mammary carcinoma cells) and NIH/3T3 (mouse fibroblast cells)<br>mouse fibroblast (L929) cell lines | [131],<br>[132] |
| 3. | PCT + SNP | Anti-cancer | A549<br>MDA-MB-231, MCF-7, 4T1, Saos-2, and on non-cancerous HUVEC cells | [133],<br>[134] |
| 4. | PCT+GNP | Anti-cancer | MCF-7 and MDA-MB 231 | [135],<br>[136] |
| 5. | 5-FLU-SNP | Anti-cancer<br>Anti-proliferative<br>Anti-bacterial | SKOV-3, MDA-MB-435 and A549 cells<br>U251 (glioma), MCF-7 (breast), NCI-ADR/RES (ovarian expressing phenotype of multiple drugs resistance), 786-O (kidney), NCI-H460 (lung, non-small cells), PC-3 (prostate), OVCAR-03 (ovarian), HT-29 (colon adenocarcinoma) and K-562 (chronic myeloid leukemia<br>S. aureus ATCC 25923<br>E. coli<br>ATCC 25922<br>P. aeruginosa ATCC 27853 | [137],<br>[138] |
| 6. | 5-FLU-GNP | Anti-cancer<br>Anti-microbial<br>Anti-fungal | MCF-7<br>and MDA-MB-231 cell lines<br>*Micrococcus luteus,*<br>*Staphylococcus aureus,*<br>*Pseudomonas aeruginosa,*<br>*Escherichia coli*<br>*Aspergillus fumigatus and*<br>*Aspergillus niger* | [139],<br>[140] |

The interaction between *DOX and SNP* was observed and tested on human breast cancer cell lines T47D (ATCC HTB133, USA) and MCF-7 (ATCC HTB-22, USA) by A. Hekmat and collaborators. They demonstrate the effect produced on structural change of DNA and that the presence of silver nanoparticles induces the cytotoxic effect of doxorubicin on MCF7 and T47D cells [129]. The study of J. Saeidi et al. evaluates the cytotoxic effect on H9c2 cell and demonstrates that an

optimum combination of DOX 0.3 μM and SNP 20 μM had a suitable effect on cancerous cells [130].

Another study shows that *DOX and GNP* interact against 4T1 (mouse mammary carcinoma cells) and NIH/3T3 (mouse fibroblast cells) cells. The DOX was released and localized within the cells, which can enhance the cytotoxicity of DOX and can be used to improve imaging contrast or for dermal cancer photo therapy [131]. D. Dhamecha et al. investigate the DOX functionalized GNP for treatment of chemically induced fibrosarcoma in mice. Thus, DOX and GNP exhibited a higher therapeutic anticancer activity as compared to doxorubicin applied alone [132].

*Paclitaxel and metallic nanoparticles* show anticancer activity against A549, MDA-MB-231, MCF-7, 4T1, Saos-2 and non-cancerous HUVEC cells. In the study of J. Zou et al., *SNP and PCT* induced A549 cell apoptosis and suppressed the growth of tumor. The anticancer activity was enhanced through ROS mediated p53 and AKT signaling pathways [133]. In the study conducted by F. Danışman-Kalındemirtaşal on MCF-7, 4T1, MDA-MB-231 and Saos-2 cells, it was observed that the conjugation of SNP with PCT was more efficient than in the application of PCT alone. It is highlighted that this combination was effective in the case of Saos-2 cells and it is concluded that this type of complex formed can be a sure candidate in the treatment of different types of cancers [134]. Regarding GNP and PCT conjugation, inhibition of cell proliferation and induction of apoptosis in MCF-7 and MDA-MB-231 cells was observed. So the complex formed can improve the anti-proliferative and anticancer potency [135, 136].

5-Fluorouracil was encapsulated in the silver nanoparticles and tested an SKOV-3, MDA-MB-435 and A549 cells. A. Garg and S. Garg treated these cells with various concentrations of combined 5-FLU+SNP (10, 20, 40, and 80 lg/mL) and the results show that the cytotoxicity induced to the tumor cells was dose dependent. When the concentration of 5-FLU was increased the viability of cells decreased [137]. J. H. B. Nunes and his research group show the antibacterial activity against Gram-positive (*Staphyloccocus aureus*) and negative (*Escherichia coli* and *Pseudomonas aeruginosa*) and also the anti-proliferative activities on nine human tumor cell lines: U251 (glioma), MCF-7 (breast), NCI-ADR/RES (ovarian expressing phenotype of multiple drugs resistance), 786-O (kidney), NCI-H460 (lung, non-small cells), PC-3 (prostate), OVCAR-03 (ovarian), HT-29 (colon adenocarcinoma) and K-562 (chronic myeloid leukemia). Among antibacterial results, a high selectivity of the complex was for the gram negative bacteria with MIC 312.5 μg $mL^{-1}$. The result shows a powerful synergy effect for ovarian multidrug resistant (0.36 μg $mL^{-1}$) and colon tumor cell (0.36 μg $mL^{-1}$) [138].

J. R. Lakkakula and his research group synthesized gold nanoparticles and then mixed them with 5-fluorouracil inclusion complex (fluorouracil and β-

cyclodextrin) and evaluated the cellular activity against MCF-7 and MDA-MB-231 cell lines. The results show that this kind of complex helps to inhibit the growth rate in MDA-MB-231 and MCF-7 breast cancer cells [139]. V. Selvaraj et al. shows that 5-FLU and GNP have antibacterial efficiency against *Micrococcus luteus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and antifungal activity against *Aspergillus fumigatus* and *Aspergillus niger* [140].

The development of complexes implying various drug interactions with metal nanoparticles or plant extracts is able to attack the cancer cell and at the same time protect the rest of the body from possible side effects. Alteration of cancer cells is due to both metal nanoparticles and other chemotherapeutic agents applied individually, but by their association, the effectiveness increases resulting in synergistic effects. The cytotoxicity of metallic nanoparticles is tested both *in vivo* and *in vitro*. The interaction with various biomolecules may be explored using the Langmuir Blodgett Technique, LBT, that can simulate the cell membrane using a single layer oriented at air/water interfaces [141]. The nano-scale interactions are a domain that needs more exploitation. However, to treat the most popular illness of human body, cancer, and other, it is important to begin from the level of self-assemblies of nanostructured materials based on collagen [142-144], fatty acids [145-148], stearic acid [149-154], proteins [155, 156], lipids [157, 158], phospholipids [159-161], galactolipids [162, 163], antioxidants [164-166], cholesterol [167, 168], lecithin [169] and drugs/local anesthetic drug [170-172]. For drugs transport, ideal candidates as nano-carrier are hydroxyapatite [173-189] and forsterite [190-197] which allow controlled drug release at the target site. The Langmuir Blodgett technique, LBT, is opening new research interests such as biomaterials or bone disease and drug delivery, biomimetic self-assembled scaffolds, regenerative medicine, tissue engineering, cancer therapy and many others, using model membranes, self-assembled at fluid interfaces at selected lateral surface pressures similar to those in biological membranes *in vivo.* It is a technique that may be useful to multiple biomedical applications.

## 6. Carotenoids and clinical applications

A special role in organs protection, cell membrane stability, photosynthesis, cellular differentiation is that of carotenoids. In the last decade they attract a special attention due to anticancer, antioxidant activity, stimulatory effect on the immune system, metabolism and other beneficial effect on human health [198-200]. Carotenoids are natural pigments produced in some plants such as vegetables, algae, fungi and bacterial species (e.g. β-carotene, lycopene, lutein, zeaxanthin, canthaxanthin) that can also prevent atherosclerosis, age-related macular degeneration and other chronic diseases [201-203].

M. Tomoaia-Cotisel and coworkers studied the carotenoids pigment by Langmuir-Blodgett Technique; they produced self-assembled and supra-molecular

structures at air/water, oil/water and benzene/water interfaces. This approach opened new potentials in monolayers and multilayers structures with biological and biomedical importance for life science [204-221].

Recent clinical research highlighted the anti-cancer effect through cell cycle arrest, inhibiting tumor growth and the reduction of cancer risk [222]. Encapsulation of carotenoids in various nano-carriers is the new strategy for cancer prevention by enhancing solubility, membrane permeation, bio accessibility and stability. The advantages are sustained release, reduced toxicity, and improved medicinal efficiency and bioavailability, increased stability. Some examples from literature are polymeric, lipid, inorganic, hybrid nano-carriers [223].

R. Niranjana and coworkers highlighted that *β-carotene* fights against human promyelocytic leukemia (HL-60) cells. The cells are arrested in the G1 phase and the viability of HL-60 cells is markedly reduced. Also it induces cell arrest in G2/M phase in human colon adenocarcinoma by reducing the expression of cyclin A [224]. ]. In the case of breast cancer MCF-7 cell line, β-carotene decreased the survival of these cells in a dose-dependent manner [225]. N. Y. Lee and his research group found in HCT116 colon cancer cell line that β-carotene inhibited cell viability, suppressed cell proliferation and the expression of certain CSC markers by acting on M2 macrophages. β-carotene also inhibited the migration, invasion and epithelial-mesenchymal transition by regulating the activation of CCD-18Co fibroblasts [226]. U. Heinrich et al. investigate the erythema-protective effect of β -carotene 24 mg/d to that of a carotenoid mix consisting in β-carotene, lycopene and lutein (8mg/d). After an additional 12 weeks with the carotenoid mixture, there is an improvement in UV-induced erythema in humans, which is comparable to β-carotene alone [227].

M. Mirahmadi and collaborators conclude in their study in vitro that *lycopene* suppresses the progression and proliferation of cells in G0/G1 phase, enhances the number of cells in S and G2/M phases and induces apoptosis by changing Bax and Ccl2 gene expression in prostate cancer. In vivo study lycopene decreased the damage of DNA, decreased the risk and growth of prostate cancer and also decreased prostate specific antigen [228]. In the study conducted by R. B. van Breemen and N. Pajkovic, lycopene is associated to decreased risk of cancers by consumption of tomato [229]. N. F. Gloria and colleagues treat with lycopene and β-carotene human breast cell lines (MCF-7, MDA-MB-231 and MDA-MB-235) with 0.5-10 μM for 48 and 96 h. Through obtained results they identified a decrease in the number of viable breast cancer cells, inhibition of cell proliferation; they arrest the cell cycle in different phases, and increase apoptosis [230].

*Lutein* is present in skin cell and protects against UV radiation. Lutein has anti-inflammatory properties and beneficial effects on the eyes. It improves age-

related macular disease and can be a safe treatment for cataracts. Y. Hu and colleagues showed in vitro experiments that lutein has the ability to prevent cataracts in bovine lens epithelial cells by inhibiting lens cell proliferation and migration at a concentration of higher or equal 1 micromol / L [231]. Y. Li and coworkers revealed through their study on the human breast cancer cell lines MDA-MB-157 and MCF-7 that lutein inhibits cell proliferation in dose-dependent manner. Lutein suppresses the viability, invasion and migration of cells by decreasing HES1 expression, induces the apoptosis of breast cancer cells under normoxia and hypoxia [232]. Together with *zeaxanthin* it protects human lens cell and rat kidney fibroblast. Through the antioxidant and photo-protective activity lutein and zeaxanthin may reduce oxidative metabolites; in mice it causes significant reductions in apoptotic keratinocytes, decreases the erythema induced by UV-light and resistance to degradation due to oxidative stress [233]. It also protects the eye against degenerative conditions and cataract if keeping an adequate and appropriate diet [234]. The retina exposed to blue light causes oxidative stress, mitochondrial and inflammatory apoptosis, DNA damage that finally leads to glaucoma, keratitis and dry eye disease. Reactive oxygen species cause cellular damage and promote the aging process in retina. The two xanthopills located in the lipid bi-layer of retinal membrane are able to protect the retina from triggers of ophthalmological diseases. These are described by specialized literature as oriented perpendicular to the bilayer surface. The HR-LBP is the binding protein of lutein and GSTP1 is the binding protein for zeaxanthin. Both binding proteins associated to membrane are found in human macula [235, 236].

*Canthaxanthin* is a natural colorant that was reported to act as an anti-cancer agent in WiDr colon adenocarcinoma and SK-MEL-2 melanoma cells. In a study conducted by P. Palozza and coworkers the obtained results show an inhibition in both cells and apoptosis was induced [237]. This molecule has the ability to treat chronic diseases such as retinal dystrophy and aplastic anemia [238]. It can be incorporated in model lipid membrane using Langmuir Blodgett Technique [239-241]. A. P. Surai and coworkers study the canthaxanthin supplementation of developing chick diet. They show 5 diets such as controlled low xanthophyll diet, or the same diet supplemented with 3, 6, 12 or 24 mg/kg canthaxanthin. First the canthaxanthin is accumulated in the egg yolk and then with supplementation is transferred to the developing embryo. Finally, the results show that carotenoids can modulate the antioxidant system of developing chicken [242].

Carotenoids are molecules with important potential in the treatment of various chronic diseases. The literature has demonstrated through studies of researchers their role in daily diet, nano-science and medicine. Carotenoids together with other biomolecules obtained from plants are effective in the

biological system, of course properly consumed and applied in optimal doses for the treatment of diseases. By eating fruits, vegetables and other sources that contain carotenoids we improve our immune system and balance the proper functioning of the body that will be able to fight against the triggers of disease.

## 7. Conclusions

This review is focused on biomolecules extracted from plants such as, piperine, curcumin, resveratrol and icariin and their interactions with some chemotherapeutic agent like doxorubicin, 5-fluorouracil and paclitaxel. By combining biomolecules with each other their efficiency was demonstrated in various cancer cells lines by inducing apoptosis and cytotoxic effects; they protect organs from oxidative stress and in this time of pandemic the treatment of COVID 19.

Natural pigments such as carotenoids were also discussed and their importance was highlighted in human diet, nano-science and biomedical applications, in treating various illnesses and incorporation in a model membrane through Langmuir Blodgett Technique.

The review highlighted also the combining therapy of biomolecules and chemotherapeutic drugs with metallic nanoparticles, demonstrating their efficiency on various cancer cell lines such as human colon cancer cells, breast cancer cells, human lung carcinoma, prostate cancer cell and their antibacterial and antioxidant activity.

The reaction of biomolecules on the new coronavirus has also been pointed out, but more extensive studies need to be performed. In this sense, new areas of development are foreseen to combat the effects produced by the new virus. Of course, a strategy for the development of nanostructured biomaterials is the Langmuir Blodgett technique which mimics the biological membrane and through which conclusive information would be obtained on the treatment of the multiple diseases of our century.

Through this research we wanted to highlight the importance of the environment in which we live, it must be as natural as possible so that we can benefit from the remedies that plants give us for the benefit of human health.

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## **Notations** and/or **Abbreviations**

PIP: piperine; CUC: curcumin; RES: resveratrol; ICA: icariin; DOX: doxorubicin; 5-FLU: 5-fluorouracil; PCT: paclitaxel; GNP: gold nanoparticles, AuNP; SNP: silver nanoparticles, AgNP; LBT: Langmuir-Blodgett technique.

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