

SYNERGISTIC ANTI-CANCER EFFECTS OF NATURAL PRODUCTS AND THEIR MODE OF ACTION**MONIKA GUPTA***Amity Institute of Biotechnology, Amity University, Gwalior, Madhya Pradesh, India.
Email: biotech.monikaphd@gmail.com*Received: 18 December 2020, Revised and Accepted: 19 January 2021***ABSTRACT**

Cancer has emerged as the second leading cause of death globally. There has been a lot of interest in other treatments like this. This includes hormonal supplements, radiation therapy, chemotherapy, surgery, and other medicines which are used in singles or combinations. Therefore, due to the habit of patient combination therapy, interactions of other drugs like hormonal supplements may be of great risk. Without consulting the doctor, the administration of herbal medicines by patients is growing rapidly in the whole world. There is also a possibility of herbal medicines. Extracts or herbal medicines are a combination of active ingredients that automatically interacts with other medicines to increase or reduce the therapeutic effect. This review focuses on the interactions of herbal medicines as well as on different types of nanoparticles (NPs), which are affected by various types of cancer treatment. Dietetic phytochemicals such as genestin, curcumin, epigallocatechin gallate, quercetin, and resveratrol have been given special emphasis on their working mechanism. All phytochemicals increase their therapeutic effects either by increasing the bio-availability of other drugs or by stabilizing some other medicines in the system.

Keywords: Genistein, Resveratrol, Polyphenol-rich extracts, Cancer treatment.

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INTRODUCTION

Cancer has now become a major threat to public health across the globe, and thus has become the second largest cause of deaths in the United States [1]. NCI estimates that in 2013, 16,60,290 males and females would be diagnosed of cancer and out of those, 5,80,350 males and females will die of cancer [2]. In addition to that, present cancer treatments remain costly and ineffective, especially in the advanced stages. As a result, there has been quite a lot of research which focuses on the prevention of cancer across the population. The epidemiologic analysis of almost 200 studies that observed the correlation between vegetable and fruit intake and cancer incidence, clearly showed that people having highest intake of vegetable and fruit in their diet have the lowest occurrence of cancers that includes ovary, stomach, colon, cervix, lung, oral, esophagus, breast bladder; and pancreas. Most sites had twice the risk of cancer in that of people who consumed vegetables and fruits at least in comparison with people with high intake [3]. This is mainly because these foods are rich source of many bioactive compounds and this has led researchers to focus attention on these active ingredients that are found in vegetables and fruits and also analyze the molecular mechanisms of action that targets for cancer prevention [4-8].

The active constituents found in plants were exposed to act on different and random molecular targets to restrain carcinogenesis and cancer build-up [9-11], while the individual active compound was shown as main anticancer activity agent. The up-and-coming area of research has focused on the combination of various types of nutritional compounds on cancer, which work to make synergic impact through many cell-signaling routes [12-15].

While discussing therapeutic targets of cancer it is necessary to discuss the hallmarks of cancer, which were initially recognized in a seminal paper by Hanahan and Weinberg in 2000 [16]. They determined six biological capabilities developed during tumorigenesis that gives insight into the intricate nature of cancer and targets of therapeutic action of various anti-cancer compounds. The developed hallmark of cancer are metastasis, activating attack, sustaining multiple signaling, allowing replicative immortality, escaping growth suppressors, resisting to angiogenesis, and leading to cell death. Identifying these major properties and focusing on them enables perfect efficiency on cancer treatments also specific to tumor cells.

SYNERGISTIC EFFECT OF VARIOUS PHYTOCHEMICALS


The study of synergism of many phytochemicals increases the efficiency of anticancer compounds. The ability of chemopreventive phytochemicals to avoid growth of tumor is the result of a combination of numerous sets of different intracellular effects rather than any single biological reaction [17]. Cancer frequently results in the accumulation of several mutations in the gene, resulting in normal interruption of cell indication and preservation, so it is possible that objectifying many tasks will be the result in future outcomes [18]. Numerous studies proposed that spices, vegetables, and fruits can overlap with complementary mechanism of activity that includes modulation of activity enzymes in phytochemicals, stimulation of the immune system, scavenging of oxidative agents, metabolizing hormone, cell multiplication and regulation of gene expression in apoptosis, and antiviral and antibacterial effects [18].

As a result of combination treatment may also induce therapeutic synergy between individual compounds in relevant dose, thereby reducing their individual toxicity and concentration [19]. Therapeutic dosage for individual anti-carcinogens may be naturally incorporated from sources of the plant, although the combination of several antitumorous gens at the sub-therapeutic levels has been shown as a result of significant antitumor effect [15].

DIETARY PHYTOCHEMICALS HAVE CHEMOPREVENTIVE PROPERTIES

This word "chemoprevention" was first used by Dr. Michael, who used to use chemical agents which occur naturally, to inhibit or overturn the carcinogenesis disease procedure [20]. Thirty years had passed since then, there have been numerous naturally occurring nutritional compounds that were found to acquire chemopreventive properties (Table 1) [7,18,19,21-28]. Chemopreventive techniques that use phytochemicals which are found in vegetables, fruits, spices, and tea prove to be a promising area in cancer research because they are cheap, safe, and easily available and possess a variety of inhibitory effects in metastasis, cancer initiation, and progression. Quite a lot of research has been done to explain the underlying mode of action of these phytochemicals and many cellular mechanisms have been involved in the cancer preventive effects of dietary phytochemicals that include

Table 1: List of natural compound anticancer product (anticancer activity) and mode of action

S. no.	Natural product	Natural product structure	Plant source	Native	Anticancer effect	Mode of action	Organ	References
1.	Epigallocatechin galleate		Green tea	Darjeeling, Assam	Anti-oxidant, increases hyperinsulinemia, and not allow chronic inflammation, stops cellular oxidation and free-radical damage to cells.	It suppresses PDGFR-BB signals and also restricts tyrosine phosphatases by increasing H ₂ O ₂ levels.	Liver	[19]
2.	Camptothecin		<i>Camptotheca</i> , Happy tree	Southern China and Tibet	Camptothecin is most potent during S-phase which hampers the activity of enzyme and damages DNA in presence of topoisomerase-I.	The main mechanism to kill cell by CPT is destruct in S-phase by inhibition of TopI activity by forming ternary complex acting as roadblock in DNA replication resulting in DNA breakage.	Tumors	[18]
3.	Vincristine		Periwinkle plants	Bengal	It is injected by intravenous method and hampers mitosis (preventing cell division), thus causing cell death.	Vincristine hampers division of rapid cell types in metaphase and stops mitosis. It links to tubulin dimmers and restricts formation of microtubules.	Intestine epithelium and bone marrow	[23]
4.	Curcumin		<i>Curcuma longa</i>	South West India	Reduction of, IL-8, mRNA, VEGF, COX-2, and expression of proteins, reduction in AKT and extracellular regulation of signals.	Lead to apoptosis, suppress signals of survival, remove reactive oxidative species, and develop an anti-inflammatory cancer environment.	Colon	[24]
5.	Mitomycin C		<i>Streptomyces caespitosus</i>	Micro-organism (Soil fungi)	Suppresses synthesis of DNA by creating cross-links which stops cell replication and cause apoptosis.	Mitomycin C has anti-tumor properties and strong DNA cross linker. It is achieved by reductive activation and after that 2 N-alkylations. Both of the alkylations are specifically for a sequence 5'-CpG-3'.	Upper gastrointestinal	[25]
6.	Paclitaxel (Taxol)		Pacific yew tree	Most parts of Europe, southwest Asia and .northwest Africa, Iran	Antimitotic agent, not allowing cell division.	It gets bound to tubulin, protein of microtubules thus stabilizing them, blocking cells in M phase, inhibiting cell division and hence cell death.	Breast cancer, lung cancer	[26]
7.	Quercetin		Vegetable and fruits	Globally distributed	Has highly reactive OH group that deactivates radicals.	Quercetin inhibits the cell growth and the DNA synthesis.	Salivary gland	[27]
8.	Vinblastine		<i>Vinca rosea</i>	Madagascar	Gets bound to microtubular proteins during mitosis thus stopping cell division.	Prevent cell division during M phase. Damage microtubules in cells by inhibiting microtubular polymerization.	Bladder cancer, brain cancer	[28]

proliferation of cell, inhibiting progress of cell's cycle, and antioxidant enzyme inducing apoptosis and activating genes which suppress tumor by changing pathways in cellular signaling [8,10,29].

Genistein

Genistein, a poly-phenolic compounds found in soya seeds (*Glycine soja*), in conjunction with cisplatin, increased the production of pancreatic cancer cell line BXP-3 and stimulated their apoptosis and consequent decrease of tumor growth shown *in vivo* [30,31]. Besides to all this, after the administration of intraperitoneal cisplatin supplements, Genistein and 5-fluorouracil, the regression of cancer in the C 57 B16 rats with the Lewis lung carcinoma cells was observed [32]. It was described as remarkable since in this particular experiment, pharmacotherapeutics were combined with radiotherapy.

Showed that genistein have seen decrease in expression of anti-apoptotic protein B-cell Lymphoma 2 (BCL-2) and downregulated nuclear factor kappa B (NF-KB) nuclear factor kappa-light-chain-enhancer of activated B cells and BclXL in xenografts of pancreatic cancer cells in animals fed as well as this isoflavone.

Curcumin

It is a phenolic compound which was found from the rhizome of the *Curcumin Longa L*, could also be synergized with chemotherapy. Extremely, curcumin and additional curcuminoids are one of the mainly potent polyphenols when applied in comedication with drugs of anticancer [15]. Prior studies were reported by Du *et al.* [33] which said that in connection with the 5-fluorouracil, curcumin efficiently underlines the development of HT-29 cells of colon cancer and reduces the cyclooxygenase-2 expression. In addition, 5-fluorouracil, oxaliplatin, and curcumin synergism prevented the occurrence of HT-29 cell multiplication and their apoptosis. The three combinations of the above highlighted compounds were highly effective than single curcumin or either mixed together with 5-fluorouracil. In addition, curcumin together mixed with oxaliplatin or with cisplatin, causes cell's cycle get arrested in human ovarian carcinoma 2008, and induced their apoptosis as well as in C13 cells. The interesting thing is that the combinations of these compounds were more effective than used individually [34].

Epigallocatechin gallate

The outcomes of many studies show that polyphenols in green tea extracts improve the sensitivity of cancer causing cells toward chemotherapy. It is possible that there is an association with anticancer medicines, one of the green tea's gallic acid polyphenols [15]. For example, (-) - Epigallocatechin 3-galate (EGCG), a compound of isolated tea leaves (*Camellia sinensis*), acute doxorubicin action in humans carcinoma, and KB-1-xenografts in rats [35]. EGCG increased doxorubicin concentration in xenografts by 51% as well as apoptosis in the tumor. Perhaps, EGCG inhibited the effect of the medicine from cells by changing Adenosine triphosphate hydrolysis in P-glycoprotein [36]. The useful result of EGCG has been explained in the previous studies [37], that is, the incubation of Mz-ChA-1 cells (human cholangiocarcinoma) with EGCG which is sensitized for the action of the gemcitabine, released in cytosol and depolarization of mitochondrial membrane which triggered apoptosis (Cell death). *In vivo* studies show that, EGCG reduced the development of Mz-ChA-1 cells in nude rats and improved sensitivity to the gemcitabine. The combination of EGCG and cisplatin accelerated the action of the medicine; thus, it causes oxidative stresses in the ovarian cancer cell lines (C 200, CAV3, and SKOV3) [38]. In addition, EGCG sensed glioma cells for tamoxifen and cisplatin by inhibiting telomerase expression [39].

Synergistic induction of apoptosis of cancer cells in humans prevents formation of tumors in mice and the review of the molecular mechanism under the control of tumor growth in the xenograft murine model which is made through combining anticancer medicine by EGCG or other green tea catechins which has been explained in the previous study [40].

Quercetin

It is usually a flavonol established in plants including onions explained [41], how this compound of phenolic can strengthen the action of doxorubicin in the cells of neuroblastoma to a small amount, and can absorb heat shock protein expression in the sarcoma cells of the Ewing's. Quercetin mixed with an amount of cisplatin show some proapoptotic effect in various types of human laryngeal carcinoma cells [42].

Similar kind of outcomes has been explained by Ramos and Aller [43] with the combination of arsenic trioxide and quercetin, which treated HL 60 human leukemia cells and U 937 grade. According to Du *et al.*, [44] synergism was investigated in between doxorubicin and quercetin. When the above was implanted in 4T1 breast tumor in rats, the combination of chemotherapeutic and flavonol indicated above shows the reduction in tumor growth and side effects of doxorubicin, which causes tumor-free survival of mice in the long-term. It has been a popular fact that secreted cytokines affect the immune response by Th1 and Th2 lymphocytes. Quercetin together with doxorubicin has seen an increase in the concentrations of IFN- γ and IL-2 and deficits in the concentrations of IL-10 and IL-4 in serum simultaneously [45].

Temozolomide is alkyl agent in chemotherapeutic and the human astrocytoma cell lines [46], quercetin was reported to work synergically with this drug of autophagy-induced due to necrosis.

Resveratrol

Resveratrol is related to stilbenes and is found in alcohol, soya, grapes, peanuts, and others. It is fully capable of reducing the side effects of chemotherapy. For example, the effect of resveratrol on [47], cisplatin-induced renal damage has been evaluated. Studies have been done on male Wistar rats that have been treated by resveratrol previous to the administration of cisplatin. Then, blood and urine taster were collected. Next to be done was removal of kidneys. Acute tubular cell necrosis has been seen only in the group of mice treated by cisplatin without use of resveratrol pretreatment. While, before the administration of cisplatin in the group treated by resveratrol, the lower level of creatinine in serum and proteins in urine (representative kidney wound) was reported. In spite of all this, compared to the group of mice which were traditionally treated only by cisplatin, the resveratrol reduced the amount of lipid peroxidation and enhance low glutathione (GSH) in the tissues.

In vitro studies have been passed through the previous studies [48] done on acute myeloid leukemia cells, in which resveratrol facilitates uptake of doxorubicin through cells maybe because MRP-1 can reduce the expression. It performs an energy-dependent efflux pump, in which over expression decreases the doxorubicin concentration in the cell.

Polyphenol-rich extracts

Besides, single phenolic, and polyphenols rich extract was also reported to work synergistically with anticancer chemotherapy. For example, hepatoma (HepG2) cells and an evening seed extract of primrose sensitized HTB-140 to vincristine which is a mitotic blocker in cancer chemotherapy [49]. The drug of chemotherapeutic (1 μ M) in HTB-140 and cells of HepG2 and extract (25 μ g/mL) were combined together and resulted in a four and a half fold increase in cytotoxicity, respectively, when evaluated in comparison to single vincristine usage. The extract is found to be rich in hydrolysable tannins and procyanidins essentially pentagalloyl glucose, which can make an important contribution to the observed effect.

Various sections of the compound have so far been distinguished from different components of the *Teucrium polium L (Lamiaceae)* and wild-growing flower plants that originate in abundant amounts in North Africa, Europe and South-Western Asia, and traditionally various pathogenic used in situations (including rheumatism, inflammation, gastrointestinal disorders, and diabetes) [49]. The two main types of groups contain flavonoids and terpenoids [49]. One of which is a

major compound of flavonoids and those are rutin and apigenin from *T. polium* L. extract which is prepared in a methanol solvent [50]. It has been suggested that an extract of methanolic of this plant potentiates proapoptotic effects and the cytotoxicity of three anticancer drugs (doxorubicin, vincristine, and vinblastine) have been reported from many cell lines of cancer such as A431, MCF- 7, Skmel-3, SW480, EJ, Saos-2, and KB.

Polyphenols have the main components of the above extract. For example, the typical phenolic compounds of propolis contain p-coumaric acid, naringenin, cinnamic acid, pinostrobin, caffeic acid, apigenin, pinocembrin, chrysin, kaempferol, ferulic acid, and quercetin [51].

Although, the dissimilarity in phenolic profiles was that these extracts were displayed to perform synergistically with more than one anticancer chemotherapeutics. Significantly, the synergistic effects were demonstrated not only *in vitro* but also in animal models.

ANTICANCER SYNERGY BETWEEN POLYPHENOLS

Phytochemicals found in plant extract can be synergistically interacted with each other, resulting in superior anticancer activity of extracts compared to the activity of their individual components [52].

According to Mertens-Talcott *et al.* [53], the ellagic acids and quercetin have been exposed so as to synergistically decrease the viability and multiplication and thus activate apoptosis of MOLT-4 cells (human leukemia) at concentrations of 5 and 10 μ M. Cell's cycle kinetics changed significantly as an outcome of combined treatment. According to Mertens-Talcott and Percival [50,54], tests of two other mixture of phenolics (Resveratrol + Resveratrol and Quercetin + ellagic acid) are made on similar cell lines as possible apoptosis-stimulating agents and as anti-proliferative agents. The two combinations has shown that more stabilizer connections with a little synergistic effect for the previous than for the latter.

One more research has shown that curcumin and resveratrol have synergistically inhibited the growth of both P 53-negative and P-53-positive (wild type) HCT-116 cells (human colon cancer) [55]. *In vivo* studies have shown that this mixture of phenolic compound which is strong and is useful in suppression of development of tumors (HCT-116 [WT]) in combined immunodeficiency in mice xenografts than the single agent. In the same way, the resveratrol combination has been proved with the seed extract of grape, allergy acids, and other phytochemicals to be strongly inhibiting skin tumorigenesis in SENCAR mice [47]. This resveratrol has been applied on topically. Grape seed extract was administered, and ellagic acid administered in the diet as well; one more agent which was tested during the study was calcium D-Glucarch. Importantly, all mixtures including resveratrol showed a synergistic effect against Ha-ras mutations and epidermal hyperplasia.

Synergistic effect for (Green Tea) catechins was reported, for example, the mixture of both epicatechin (1 mg/ml) and EGCG (10 mg/ml) inhibited the progress of HT-29 cells (human cancer) and gave birth to their apoptosis [56].

Synergy's performance is shown by [57] and is among the components of pomegranate juice. Extract demonstrated that high activity of antiproliferative agents against 4 colon cancer, 2 oral cancer, and 2 prostate cancer cell lines as compared to its major polyphenols and tannin extract of a standard total pomegranate.

A combination extract of coffee, thyme, cloves, walnuts, and oregano has been confirmed as a powerful modular of NF-KB which indicate both as *in vitro* and *in vivo* [58]. The prevention of lipopolysaccharide (LPS) was the activation of NF-KB synergistically through mixture extract, as was proved through evaluation with the activity of single extracts. Before LPS treatment, transgenic NF-KB luciferase reporter mice decreased in the entire body of activity of LPS-induced NF-KB after 6 h of 35% compared to control in mice. The gene expression which is related to

inflammation, liver proliferation, and cell migration was also reduced through mixture extract. Propolis is a honeybee product that has abundance of phenolic acids and flavonoids, and with its polyphenols-rich hexane extract and dichloromethane, acts as antiproliferative and cytotoxicity agents in the direction of five cell lines derived from liver (Hep G2) [59], lung (Chaco), human carcinomas breast (BT474), colon (SW620), and stomach (KATO-III).

Keeping in mind that Olive Mediterranean diet is one of the main components of the Fabiani *et al.* [50]. In the study done on human promyelocytic leukemia (HL)-60 cell lines, four complex virgin olive oils are included *in vitro* chemopreventive activities. The proapoptotic and antiproliferative activities of the extract have been categorized positively with the material of the secoiridoids. In this type of sub-group of polyphenol, oleuropein and hydroxytyrosol are the main phenolic compounds of olive oil. The important thing is that the above-mentioned anticancer activities have also been correlated negatively by the concentration of olive oil phenol compounds (i.e., lignans and two other subgroups of phenyl alcohols). The most important thing is that when a compound combination of olive oil phenolics was tested, more than one anticancer effect has been shown as compared to single compound, which is the presence of extraction of synergistic interactions and other unknown extract, antiproliferative or proapoptotic activities have been shown toward HL-60 cells.

In many Chinese medicines, *Fagopyrum cymosum* and *Rosa roxburghii* Tratt., improving immune response reactions and enhancing digestive power, have proved to be more effective as antigigant agents. Studies have been done on the *in vitro* anticancer activity of their extraction (pulmonary carcinoma A549, CaEs-17 esophageal squamous carcinoma, and SGC-7901 gastric carcinoma), combination of extract of both plant causes an increase in apoptosis.

EFFECT OF NANOMEDICINE FOR CANCER TREATMENT

There are some limitations in cancer treatment, regarding metals that can be used for cancer treatment, such as Gold, Silver, Iron, Zinc, and Carbon nano tube as seen in Table 2 [60-76].

Zinc oxide NPs (ZnO NPs)

ZnO NPs are very much efficient and may be used to treat three types of cancer cells: (i) Human lung adenocarcinoma A459, (ii) human hepatocellular carcinoma HepG2, and (iii) human bronchial epithelial BEAS-2B. During treatment by ZnO NPs, characterizing on normal rate cells and to eliminate all the three kinds of cancer cells, mammalian shows different effects on cell feasibility such as hepatocytes and

Table 2: Various nanoparticles with size and application in cancer treatment

Types of nanoparticles	Approximate size	Application in specific organ cancer
Zinc oxide nanoparticles	50–57 nm	Breast cancer [60] Lung cancer [60] Liver cancer [61]
Gold nanoparticles	90–130 nm	Breast cancer [63] Lung cancer [64] Liver cancer [64]
Silver nanoparticles	300–700 nm	Liver cancer [67] Prostate cancer [68] Breast cancer [65]
Carbon nano tube	200–550 nm	Cervical cancer [69,70] Bladder cancer [71] Ovarian cancer [66]
Graphene nanoparticles	200–250 nm	Brain cancer [72] Ovarian cancer [73] Skin cancer [74]
Iron oxide nanoparticles	5–30 nm	Breast cancer [75] Tumor imaging [76]

astrocytes. The toxicity of ZnO NPs is diagnosed using human liver cancer HepG2 cells, which are due to the instability of toxic effects compounds [60-62].

Gold NPs (Au NPs)

Au NPs are needed as biocompatible materials for medical uses. Approximately size of 1–100 nm NPs, NPs can be given injection in vein for targeted drug treatment. In the cell, specific Au NPs will be attached to the desired antibody [63,64]. Thus, there is no side effect on using less medicine. These types of cancer cells help to absorb substantial concentrations of NPs as compared to nearby tissues [77,78].

Silver NPs (Ag NPs)

Ag NPs are recently gaining popularity as cancer treatment agents. They are very efficient compared to other nanomaterials because of their toxicity which results in killing cancer cells [79]. They are extremely fatal for Dalton's Lymphoma Ascites cells. *Catharanthus roseus* is the naturally occurring source that is mostly used to synthesize AgNPs. This plant is used in the treatment of breast cancer as traditional medicines [65]. Injecting AgNPs into cancer cells, they would react with cancer cells and deactivate them. The risk of cancer decreases largely after injecting AgNPs for at least 4–5 times. Although this is a slow process, it can be assumed that can treat cancerous cells [80].

Carbon nanotubes

Carbon nanotubes are made from a carbon graphene sheet. Carbon nanotubes have applications in all streams of engineering which develop latest generation devices such as nanofiber, nanoneedles, and nanodots. Single-walled carbon nanotubes with tumor-targeting process are implemented chemically with the use of bio-compatibility, which is collected in rats and is displayed during cancer therapy [81]. This reduces toxicity and excretion of tumor cells. A multi-walled carbon nanotubes array is embedded in a highly-sensitive DNA detector. Hence, the drug delivery system based on carbon nanotubes is used as a high efficiency treatment process having few side effects [66].

Graphene NPs

Graphene NPs uses carbon like graphite is done primarily to prevent cancer, and it has a disadvantage of radiation or chemotherapy, but cannot damage the healthy cells. After each treatment, due to cancer stem cells, drug resistance, tumors, some reproducing cells are found. When cancer stem cells are converted into tumor-globular tissue, they develop stress-resistance around them and rapidly split. Graphite oxide has soluble properties and thus dissolves in many solvents. Graphene oxide has been used in many types of cancer, such as cancers of skin, lung, pancreatic, ovarian, breast, brain, and prostate [82]. Graphene oxide turns from active cancer stem cell into a non-cancerous cell which prevents even from becoming a tumor in the future. In the treatment of cancer primarily, coated nanography sheet with polyethylene glycol can be used. Graphene is used in many areas such as nanotechnology, electronics, and biomedical [81,82].

MECHANISM OF EFFECT OF METAL NPS (M-NPS) ON CANCER CELLS

M-NPs demonstrated potent antimicrobial efficacy because of their positive charge on the metal ion, shape, and size which provides the large surface area to volume ratio. Thus, it has greater penetration, thereby accumulating inside the bacterial membrane and destroying those cells [83]. The release of M^+ ion and M^0 onto the surface from M-NPs results in diffusion inside the cell which is also termed as endocytosis. This causes mitochondrial dysfunction. Then they interact with the protein of the cell membrane and activate signaling pathways which generate reactive oxygen species (ROS). Due to strong affinity of M for sulfur, damage of proteins and nucleic acids initiates. Hence, it finally causes apoptosis and hampers the cell proliferation (Fig. 1). Thus, M-NPs create alterations in cell morphology, decreases metabolic activity inside the cell, and viability of cell diminishes [84].

M-NPs are induced into the path of mitochondria through the decrease in the levels of GSH (glutathione), more lipid peroxidation. DNA damage

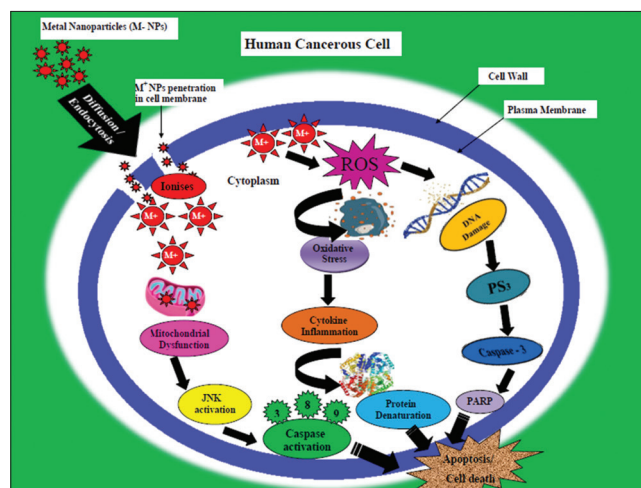


Fig. 1: Schematic diagram of mechanism of action of metal nanoparticles on human cancer cell (adapted and modified)

and apoptosis are caused by ROS responsive genes expression and regulation of pro-inflammatory cytokines [83,84].

O_2 and H_2O_2 can act as ROS species which damages proteins and lipids as well as destruct their DNA and thereby collapsing the anti-oxidant defense system. Higher amount of ROS results in increased oxidative stresses, that is, more toxicity is induced, which, in turn, reduces the activity of anti-oxidant enzymes and decreases GSH level and activates caspase-3. All of these promote apoptosis by p-53 signaling pathway. It has also been observed that increase in ROS denatures various anti-apoptotic proteins and triggers different protein expressions that would ultimately lead to apoptosis [84].

Mitochondria are the epicenter for apoptosis signal. M-NPs cause a significant decrease in the permeability of mitochondrial membrane. This may result in Jun amino-terminal kinases induced apoptosis which was initiated by enhanced flow of caspase-3 and caspase-9 [83,84].

In summary, M-NPs can cause cell death through different types of processes including ROS generation, developing oxidative stresses, oxidation of GSH to glutathione disulfide (GSSG), DNA damage, activation of caspases, and mitochondrial dysfunction and disruption of enzymes [83].

CONCLUSION

The outcomes of *in vivo* and *in vitro* studies have been described briefly in the literature and it has been indicated that polyphenols-rich extracts and phenolics compounds have a more probable aspect to act as therapeutic agents that would also be chemo preventive in nature. In case of extracts, and in addition to their complementary biological activities, they have proven potential results from various phenolic and in natural proportion of synergistic interactions among them. Among others, the increasing interest of biological activities of polyphenols, there is a need to find increasing incidence of civilization diseases and then develop effective and safe process of prophylaxis and therapy also. Literature data show that there are several mechanisms which are essential for the activity of anticancer polyphenols, for example, inhibition of signal transduction pathways, above regulation of tumor suppressor genes, cell cycle arrest, also downregulation of oncogenes, impairment of angiogenesis, induction of differentiation, and apoptosis induction. It is probable to decide the suitable anticancer agent with these different modes of action performed through phenolic compounds.

Prevention therapy has a more beneficial strategy than a potential patient approach, and the utilization of usual chemoprevention agents can bear fewer risks and being environment-friendly in terms

of unfavorable side effects, less expensive, and advantage of being synthetic medicine. On the contrary, it is worth mentioning that in clinical test so far, some cases of polyphenols overdose and correlated toxicity were reported. Consequently, it is necessary to develop a set of proper biomarkers, as well as to make accurate monitoring of the properties of phenolic compounds in the treatment of cancer and chemoprevention.

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AUTHOR'S CONTRIBUTION

MG performed all the experiments and wrote the manuscript draft and design the concept and finalized the manuscript.

CONFLICT OF INTERESTS

The authors confirm they have no conflict of interests.

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REFERENCES

- Hoyert DL, Xu J. Deaths: Preliminary data for 2011. *Natl Vital Stat Rep* 2012;61:1-51.
- Howlander N, Noone AM, Krapcho MS, Neyman N, Aminou R, Altekruse SF, *et al.* SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute; 2012. p. 1975-2009. Available from: https://www.seer.cancer.gov/csr/1975_2009_pops09.
- Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr Cancer* 1992;18:1-29.
- Aggarwal B, Prasad S, Sung B, Krishnan S, Guha S. Prevention and treatment of colorectal cancer by natural agents from mother nature. *Curr colorectal Cancer Rep* 2013;9:37-56.
- Dragsted LO, Strube M, Larsen JC. Cancer-protective factors in fruits and vegetables: Biochemical and biological background. *Pharmacol Toxicol* 1993;72:116-35.
- Gullett NP, Amin AR, Bayraktar S, Pezzuto JM, Shin DM, Khuri FR, *et al.* Cancer prevention with natural compounds. *Semin Oncol* 2010;37:258-81.
- Kwon KH, Barve A, Yu S, Huang MT, Kong AN. Cancer chemoprevention by phytochemicals: Potential molecular targets, biomarkers and animal models. *Acta Pharmacol Sin* 2007;28:1409-21.
- Manson MM. Cancer prevention-the potential for diet to modulate molecular signalling. *Trends Mol Med* 2003;9:11-8.
- Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol* 2006;71:1397-421.
- Surh YJ. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer* 2003;3:768-80.
- Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: A review. *J Am Diet Assoc* 1996;96:1027-39.
- Manikandan R, Beulaja M, Arulvasu C, Sellamuthu S, Dinesh D, Prabhu D, *et al.* Synergistic anticancer activity of curcumin and catechin: An *in vitro* study using human cancer cell lines. *Microsc Res Tech* 2012;75:112-6.
- Hwang JT, Lee YK, Shin JI, Parkb OJ. Anti-inflammatory and anticarcinogenic effect of genistein alone or in combination with capsaicin in TPA-treated rat mammary glands or mammary cancer cell line. *Ann N Y Acad Sci* 2009;1171:415-20.
- Liu RH. Potential synergy of phytochemicals in cancer prevention: Mechanism of action. *J Nutr* 2004;134 Suppl 12:3479S-85S.
- de Kok TM, van Breda SG, Manson MM. Mechanisms of combined action of different chemopreventive dietary compounds: A review. *Eur J Nutr* 2008;47:51-9.
- Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57-70.
- Ashraf MA. Phytochemicals as potential anticancer drugs: Time to ponder nature's bounty. *Biomed Res Int* 2020;2020:8602879.
- Liu LF, Desai SD, Li TK, Mao Y, Sun ME, Sim SP. Mechanism of action of camptothecin. *Ann N Y Acad Sci* 2000;922:1-10.
- Toews ML, Bylund DB. Pharmacologic principles for combination therapy. *Proc Am Thorac Soc* 2005;2:282-9.
- Sporn MB, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by Vitamin A and its synthetic analogs (retinoids). *Fed Proc* 1976;35:1332-8.
- Sporn MB. Chemoprevention of cancer. *Lancet* 1993;342:1211-3.
- Bommareddy A, Eggleston W, Prelewicz S, Antal A, Witczak Z, Mccune DF, *et al.* Chemoprevention of prostate cancer by major dietary phytochemicals. *Anticancer Res* 2013;33:4163-74.
- Stanton RA, Gernert KM, Nettles JH, Aneja R. Drugs that target dynamic microtubules: A new molecular perspective. *Med Res Rev* 2011;31:443-81.
- Park W, Amin AR, Chen ZG, Shin DM. New perspectives of curcumin in cancer prevention. *Cancer Prev Res (Phila)* 2013;6:387-400.
- Tomasz M, Palom Y. The mitomycin bioreductive antitumor agents: Cross-linking and alkylation of DNA as the molecular basis of their activity. *Pharmacol Ther* 1997;76:73-87.
- Yvon AM, Wadsworth P, Jordan MA. Taxol suppresses dynamics of individual microtubules in living human tumor cells. *Mol Biol Cell* 1999;10:947-59.
- Jeong JH, An JY, Kwon YT, Rhee JG, Lee YJ. Effects of low dose quercetin: Cancer cell-specific inhibition of cell cycle progression. *J Cell Biochem* 2009;106:73-82.
- Panda D, Rathinasamy K, Santra MK, Wilson L. Kinetic suppression of microtubule dynamic instability by griseofulvin: Implications for its possible use in the treatment of cancer. *Proc Natl Acad Sci USA* 2005;102:9878-83.
- Chen C, Kong AN. Dietary cancer-chemopreventive compounds: From signaling and gene expression to pharmacological effects. *Trends Pharmacol Sci* 2005;26:318-26.
- Bahramikia S, Yazdanparast R. Phytochemistry and medicinal properties of *Teucrium polium* L. (*Lamiaceae*). *Phytother Res* 2012;26:1581-93.
- Lohse I, Brothers SP. Pathogenesis and treatment of pancreatic cancer related pain. *Anticancer Res* 2020;40:1789-96.
- Chan MM, Soprano KJ, Weinstein K, Fong D. Epigallocatechin-3-gallate delivers hydrogen peroxide to induce death of ovarian cancer cells and enhances their cisplatin susceptibility. *J Cell Physiol* 2006;207:389-96.
- Du B, Jiang L, Xia Q, Zhong L. Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. *Chemotherapy* 2006;52:23-8.
- Du G, Lin H, Wang M, Zhang S, Wu X, Lu L, *et al.* Quercetin greatly improved therapeutic index of doxorubicin against 4T1 breast cancer by its opposing effects on HIF-1 α in tumor and normal cells. *Cancer Chemother Pharmacol* 2010;65:277-87.
- Du G, Lin H, Yang Y, Zhang S, Wu X, Wang M, *et al.* Dietary quercetin combining intratumoral doxorubicin injection synergistically induces rejection of established breast cancer in mice. *Int Immunopharmacol* 2010;10:819-26.
- Fabiani R, Sepporta MV, Mazza T, Rosignoli P, Fuccelli R, de Bartolomeo A, *et al.* Influence of cultivar and concentration of selected phenolic constituents on the *in vitro* chemopreventive potential of olive oil extracts. *J Agric Food Chem* 2011;59:8167-74.
- Jaszewska E, Kosmider A, Kiss AK, Naruszewicz M. *Oenothera paradoxa* defatted seeds extract containing pentagalloylglucose and procyanidins potentiates the cytotoxicity of vincristine. *J Physiol Pharmacol* 2010;61:637.
- Kowalczyk MC, Kowalczyk P, Tolstykh O, Hanausek M, Walaszek Z, Slaga TJ. Synergistic effects of combined phytochemicals and skin cancer prevention in SENCAR mice. *Cancer Prev Res (Phila)* 2010;3:170-8.
- Kuhar M, Imran S, Singh N. Curcumin and quercetin combined with cisplatin to induce apoptosis in human laryngeal carcinoma Hep-2 cells through the mitochondrial pathway. *J Cancer Mol* 2007;3:121-8.
- Lang M, Henson R, Braconi C, Patel T. Epigallocatechin-gallate modulates chemotherapy-induced apoptosis in human cholangiocarcinoma cells. *Liver Int* 2009;29:670-7.
- McDonnell CO, Holden G, Sheridan ME, Foley D, Moriarty M, Walsh TN, *et al.* Improvement in efficacy of chemoradiotherapy by addition of an antiangiogenic agent in a murine tumor model. *J Surg Res* 2004;116:19-23.
- Mertens-Talcott SU, Percival SS. Ellagic acid and quercetin interact

- synergistically with resveratrol in the induction of apoptosis and cause transient cell cycle arrest in human leukemia cells. *Cancer Lett* 2005;218:141-51.
43. Mertens-Talcott SU, Talcott ST, Percival SS. Low concentrations of quercetin and ellagic acid synergistically influence proliferation, cytotoxicity and apoptosis in MOLT-4 human leukemia cells. *J Nutr* 2003;133:2669-74.
 44. Mohammad RM, Banerjee S, Li Y, Aboukameel A, Kucuk O, Sarkar FH. Retracted: Cisplatin-induced antitumor activity is potentiated by the soy isoflavone genistein in BxPC-3 pancreatic tumor xenografts. *Cancer* 2006;106:1260-8.
 45. Montopoli M, Ragazzi E, Froidi G, Caparrotta L. Cell-cycle inhibition and apoptosis induced by curcumin and cisplatin or oxaliplatin in human ovarian carcinoma cells. *Cell Prolif* 2009;42:195-206.
 46. Paur I, Balstad TR, Kolberg M, Pedersen MK, Austenaa LM, Jacobs DR, et al. Extract of oregano, coffee, thyme, clove, and walnuts inhibits NF-kappaB in monocytes and in transgenic reporter mice. *Cancer Prev Res (Phila)* 2010;3:653-63.
 47. Pfundstein B, El Desouky SK, Hull WE, Haubner R, Erben G, Owen RW. Polyphenolic compounds in the fruits of Egyptian medicinal plants (*Terminalia bellerica*, *Terminalia chebula* and *Terminalia horrida*): Characterization, quantitation and determination of antioxidant capacities. *Phytochemistry* 2010;71:1132-48.
 48. Qian F, Wei D, Zhang Q, Yang S. Modulation of P-glycoprotein function and reversal of multidrug resistance by (-)-epigallocatechin gallate in human cancer cells. *Biomed Pharmacother* 2005;59:64-9.
 49. Rajabalian S. Methanolic extract of *Teucrium polium* L. potentiates the cytotoxic and apoptotic effects of anticancer drugs of vincristine, vinblastine and doxorubicin against a panel of cancerous cell lines. *Exp Oncol* 2008;30:133-8.
 50. Ramos AM, Aller P. Quercetin decreases intracellular GSH content and potentiates the apoptotic action of the antileukemic drug arsenic trioxide in human leukemia cell lines. *Biochem pharmacol* 2008;75:1912-23.
 51. Seeram NP, Adams LS, Henning SM, Niu Y, Zhang Y, Nair MG, et al. *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J Nutr Biochem* 2005;16:360-7.
 52. Shervington A, Pawar V, Menon S, Thakkar D, Patel R. The sensitization of glioma cells to cisplatin and tamoxifen by the use of catechin. *Mol Biol Rep* 2009;36:1181-6.
 53. Shimizu M, Deguchi A, Lim JT, Moriwaki H, Kopelovich L, Weinstein IB. (-)-Epigallocatechin gallate and polyphenon E inhibit growth and activation of the epidermal growth factor receptor and human epidermal growth factor receptor-2 signaling pathways in human colon cancer cells. *Clin Cancer Res* 2005;11:2735-46.
 54. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10-29.
 55. Siveen KS, Kuttan G. Role of macrophages in tumour progression. *Immunol Lett* 2009;123:97-102.
 56. Suganuma M, Saha A, Fujiki H. New cancer treatment strategy using combination of green tea catechins and anticancer drugs. *Cancer Sci* 2011;102:317-23.
 57. Tai CJ, Wang CK, Tai CJ, Lin YF, Lin CS, Jian JY, et al. Aqueous extract of *Solanum nigrum* leaves induces autophagy and enhances cytotoxicity of cisplatin, doxorubicin, docetaxel, and 5-fluorouracil in human colorectal carcinoma cells. *Evid Based Complement Alternat Med* 2013;2013:514719.
 58. Teerasripreecha D, Phuwapraisirisan P, Puthong S, Kimura K, Okuyama M, Mori H, et al. *In vitro* antiproliferative/cytotoxic activity on cancer cell lines of a cardanol and a cardol enriched from Thai *Apis mellifera* propolis. *BMC Complement Altern Med* 2012;12:27.
 59. Thomasset SC, Berry DP, Garcea G, Marczylo T, Steward WP, Gescher AJ. Dietary polyphenolic phytochemicals-promising cancer chemopreventive agents in humans? A review of their clinical properties. *Int J Cancer* 2007;120:451-8.
 60. Selvakumari D, Deepa R, Mahalakshmi V, Subhashini P, Lakshminarayan N. Anti cancer activity of ZnO nanoparticles on MCF7 (breast cancer cell) and A549 (lung cancer cell). *ARPN J Eng Appl Sci* 2015;10:5418-21.
 61. Ahmad J, Ahamed M, Akhtar MJ, Alrokayan SA, Siddiqui MA, Musarrat J, et al. Apoptosis induction by silica nanoparticles mediated through reactive oxygen species in human liver cell line HepG2. *Toxicol Appl Pharmacol* 2012;259:160-8.
 62. Rasmussen JW, Martinez E, Louka P, Wingett DG. Zinc oxide nanoparticles for selective destruction of tumor cells and potential for drug delivery applications. *Expert Opin Drug Deliv* 2010;7:1063-77.
 63. Lee J, Chatterjee DK, Lee MH, Krishnan S. Gold nanoparticles in breast cancer treatment: Promise and potential pitfalls. *Cancer Lett* 2014;347:46-53.
 64. Rajeshkumar S. Anticancer activity of eco-friendly gold nanoparticles against lung and liver cancer cells. *J Genet Eng Biotechnol* 2016;14:195-202.
 65. Mridula P, Deepa M, Sreelakshmy V. Green synthesis of silver nanoparticles from *Catharanthus roseus* for breast cancer therapy. *Int J Res Dev Pharm Life Sci* 2016;5:2278.
 66. Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM. A new era of cancer treatment: Carbon nanotubes as drug delivery tools. *Int J Nanomed* 2011;6:2963.
 67. Prasannaraj G, Venkatachalam P. Green engineering of biomolecule-coated metallic silver nanoparticles and their potential cytotoxic activity against cancer cell lines. *Adv Nat Sci* 2017;8:025001.
 68. Ishida T. Anticancer activities of silver ions in cancer and tumor cells and DNA damages by Ag⁺-DNA base-pairs reactions. *MOJ Tumor Res* 2017;1:3.
 69. Viens LJ, Henley SJ, Watson M, Markowitz LE, Thomas CC, Thompson TD, et al. Human papillomavirus-associated cancers-United States, 2008-2012. *MMWR Morb Mortal Wkly Rep* 2016;65:661-6.
 70. Wu A, Zeng Q, Kang TH, Peng S, Roosinovich E, Pai SI, et al. Innovative DNA vaccine for human papillomavirus (HPV)-associated head and neck cancer. *Gene Ther* 2011;18:304-12.
 71. Hampel S, Kunze D, Haase D, Krämer K, Rauschenbach M, Ritschel M, et al. Carbon nanotubes filled with a chemotherapeutic agent: A nanocarrier mediates inhibition of tumor cell growth. *Nanomedicine (Lond)* 2008;3:175-82.
 72. Lu YJ, Yang HW, Hung SC, Huang CY, Li SM, Ma CC, et al. Improving thermal stability and efficacy of BCNU in treating glioma cells using PAA-functionalized graphene oxide. *Int J Nanomedicine* 2012;7:1737-47.
 73. Zhang XF, Gurunathan S. Combination of salinomycin and silver nanoparticles enhances apoptosis and autophagy in human ovarian cancer cells: An effective anticancer therapy. *Int J Nanomedicine* 2016;11:3655-75.
 74. Orthaber K, Pristovnik M, Skok K, Perić B, Maver U. Skin cancer and its treatment: Novel treatment approaches with emphasis on nanotechnology. *J Nanomater* 2017;2017:2606271.
 75. Poller JM, Zaloga J, Schreiber E, Unterweger H, Janko C, Radon P, et al. Selection of potential iron oxide nanoparticles for breast cancer treatment based on *in vitro* cytotoxicity and cellular uptake. *Int J Nanomed* 2017;12:3207-20.
 76. Peng XH, Qian X, Mao H, Wang AY. Targeted magnetic iron oxide nanoparticles for tumor imaging and therapy. *Int J Nanomed* 2008;3:311-21.
 77. Huang X, Jain PK, El-Sayed IH, El-Sayed MA. Plasmonic photothermal therapy (PPTT) using gold nanoparticles. *Lasers Med Sci* 2008;23:217-28.
 78. Lara Y, Thanh NT, Loizidou M, Seifalian AM. Toxicology and clinical potential of nanoparticles. *Nano Today* 2011;6:585-607.
 79. Huy TQ, Huyen PT, Le AT, Tonezzer M. Recent advances of silver nanoparticles in cancer diagnosis and treatment. *Anticancer Agents Med Chem* 2019;19:1276-87.
 80. Jeyaraj M, Sathishkumar G, Sivanandhan G, MubarakAli D, Rajesh M, Arun R, et al. Biogenic silver nanoparticles for cancer treatment: An experimental report. *Colloids Surf B Biointerfaces* 2013;106:86-92.
 81. Pinank K, Kaushik B, Shyam V, Amrutia M, Faldu NU. Revolutionary therapies and manipulation of nanoparticles to cure cancer. *J Bioelectron Nanotechnol* 2016;1:5.
 82. Vinogradov S, Wei X. Cancer stem cells and drug resistance: The potential of nanomedicine. *Nanomedicine (Lond)* 2012;7:597-615.
 83. Akter M, Sikder MT, Rahman MM, Ullah AA, Hossain KF, Banik S, et al. A systematic review on silver nanoparticles-induced cytotoxicity: Physicochemical properties and perspectives. *J Adv Res* 2017;9:1-16.
 84. Barabadi H, Ovais M, Shinwari ZK, Saravanan M. Anti-cancer green bionanomaterials: Present status and future prospects. *Green Chem Lett Rev* 2017;10:285-314.