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RESEARCH ARTICLE

SYNERGISTIC ACTIVITY OF PLANT BASED BIOACTIVES IN COMBATING CANCER: AN OVERVIEW.

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Abstract

Cancer is one of the most prevalent diseases in the world having no measure for its complete cure once it reaches its mature stage. But it can be prevented by maintaining a healthy weight, eating plenty of green leafy vegetables, fruits and whole grains, being vaccinated against certain infectious diseases and avoiding too much exposure to UV radiations and carcinogens. The available treatments for cancer ranges from surgery to radiotherapy, chemotherapy, hormone therapy, biological therapies, and even bone marrow stem cell transplants, but they all possess some side effects and limitations. Hence, plant based bioactives and other natural therapies are gaining interest as novel means of cancer prevention and treatment. Polyphenols, isothiocyanates, anthocyanins, flavonoids, phytoestrogens etc. are some of the plant based bioactives having antioxidant efficacy thus are the prime targets of investigation for potencies against various ailments including cancer. However, in spite of the anticancer efficacies of plant based bioactives, a substantial prevention or cure of cancer has not been proposed till date. Hence, combinatorial drug therapy has been used which produces effects that are more than the effects predicted from their summated individual potencies, which is defined as synergy. Synergy is an abstract concept that refers to a result that arises from interacting processes in order to treat cancer and the synergistic activity can be analyzed by various means such as isobologram. In this review paper, available drug combinations targeting cancer, has been discussed with emphasis on plant based bioactives, their synergistic potential and mechanism of action. Moreover, the direction towards developing more effective combinations targeting cancer has also been highlighted.

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Introduction:-

Cancer is one of the most prevalent diseases in the world. According to WHO estimates for 2011, cancer causes more deaths than all coronary artery diseases and stroke. The estimates of worldwide incidence and mortality for all cancer combined for 2012 states that there were overall 14.1 million new cases of cancer and 8.2 million deaths in 2012. The number is increasing every year and there is no robust and full-proof measure found till date. The most commonly diagnosed cancers are lung cancer (1.82 million), breast cancer (1.67 million) and colorectal cancer (1.36 million) [1]. In 2020, it is expected that there will be more than 16 million cancer cases diagnosed and more than 10

million deaths worldwide [2]. Looking at any particular cancer, liver cancer remains the fifth most common malignancy in men and eighth in women. The number of new cases is estimated to be 5,64,000 per year, which includes 3,98,000 in men and 1,66,000 in women while the incidence of liver cancer is increasing day by day in various developing and developed countries and this increase will likely to continue for some decades [3, 4]. In low and middle- income countries, the incidence of breast cancer is increasing by as much as 5% per year while globally, three- fourth of deaths occur due to breast cancer [5, 6]. Testicular Cancer (TC) accounts for only 1% of all male cancers [7, 8]. The current global incidence is 6.3 cases per 1, 00,000 per year with the highest rate in Northern Europe (Norway 9.6/1, 00, 000 per year) and the lowest in Asia and Africa (0.2-1/ 1,00,000 per year). While the worldwide incidence has more than double in the past 40 years, the mortality rate is low with an overall cure rate of 90-95% [9]. In developed countries, it has been observed that ovarian cancer ranks fifth in incidence (99,752 cases per year) and sixth in mortality (65,892 deaths per year) for malignant tumors among women [10]. There is a rapid worldwide increase in the incidence of Keratinocyte Cancer (KC) which has been observed in recent decades, increasing 3- 8% per year in white populations throughout Europe, USA, Canada and Australia [11].

It is evident that yearly rate of cancer incidences are increasing at every corner of this globe without much resistance because till now the biomedical science did not able to provide human civilization with any treatment for the complete cure or prevention for this deadly menace. However, some of the fruitful treatments are available for cancer though they have several limitations. These treatments include radiotherapy, chemotherapy and surgery. Radiotherapy involves the usage of high-energy radiation that damages the cancer cells. This stops the cells from dividing properly and as a result they are destroyed. The obvious risk involved in radiotherapy is that the radiations may destroy normal cells as well. In order to minimize the side effects of radiotherapy, synthetic drugs are used which are the substances that are produced entirely from chemical reactions in laboratory. Their chemical structure is identical to the naturally occurring drugs such as cocaine and opium but they are designed to enhance effects from naturally occurring drugs or to prevent side effects that are unwanted. Drugs are one of the most important tools for fighting diseases but the disadvantages of drugs should be clearly understood to ensure their effective and responsible use. Thus, it is important to define drugs in context of something that is ingested by patient to achieve a certain pleasurable or disease mitigating effect. Though chemotherapy has many advantages compared to other therapies it equally has disadvantages too [12]. Drugs are designed to alter normal body chemistry, hence, has many side effects including nausea, vomiting, upset stomach, skin irritation etc. Moreover, because of their clinical strength, these powerful artificial chemicals after entering into the body can upset body chemistry, alter the way body functions and introduce foreign substances that may not only lead to adverse effects but may also cause mutation which can result in the development of other diseases. Thus, drugs from plant or any other natural origin is getting more importance.

In addition, these prevalent treatments are not advanced enough for the complete cure of cancer and stopping its reoccurrence. They also have limitations and side effects; hence there is a need of natural drugs with no/lesser side effects. To that end, hunt for natural/plant based bioactives having anticancer efficacy is going on for a long period of time. Several success to that front have already been reported such as inhibitory effects of epigallocatechin-3-gallate (EGCG) on metastasis-associated 67 kD laminin (67LR) [13] and/or anticancer potential of sulforaphane mainly in prostate and GI cancer. However, in spite of anticancer efficacies of natural/plant based bioactives, a formula for complete cure/prevention/restriction of cancer incidence is yet to be enunciated.

A new trend set by the cancer researchers of this era towards this path is combinatorial therapy using two or more drugs irrespective of their source. The simplified idea behind this therapy is that the drug combinations (at appropriate concentrations) will produce effects that are more than the effects predicted from their summated individual potencies, defined as synergy. Technically, synergy is an abstract concept that refers to a result that arises from interacting processes. It can be defined as the creation of whole that is greater than the simple sum of its parts. The meaning can be given as working together. This can be best explained by the graph called Isobologram. Isobologram is the graphical representation of the two or more drugs which gives the individual and combined effect of the both drugs. The theoretical basis for the combination index (CI)-Isobologram equation that allows quantitative determination of drug interactions, where $CI < 1$, $= 1$, and > 1 indicate synergism, additive effect, and antagonism, respectively. Based on these algorithms, computer software has been developed to allow automated simulation of synergism and antagonism at all dose or affect levels [14]. Synergy mainly depends on the additive of two drugs. This is appropriate when both drugs act on the same system, so maximum response provoked by both drugs is same. The rule is that the natural response of combination of two drugs equals sum of two fractional responses minus their product. If the fractional response to drug A alone at any particular dose is F_a then for drug B alone it is F_b . The

additional response to drug B is the fraction F_b times the remaining possible response, which is $1 - F_a$, so the additional response due to drug B, in presence of drug A equals $F_b(1 - F_a)$. Therefore the total response to a mixture of two drugs is $F_a + F_b(1 - F_a) = F_a + F_b - F_a F_b$. This equation assumes that the effects of two drugs is additive. Below is an example of data that is shown in the form of isobologram [15].

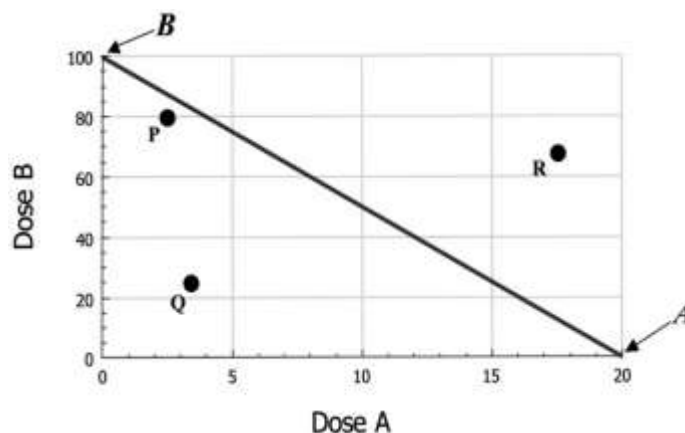


Figure: 1 Isobologram for some particular effect (e.g., 50% of the maximum) in which the dose of drug A alone is $A = 20$ and drug B alone is $B = 100$. The straight line connecting these intercept points (additivity line) is the locus of all dose pairs that, based on these potencies, should give the same effect. An actual dose pair such as point Q attains this effect with lesser quantities and is superadditive (synergistic), while the dose pair denoted by point R means greater quantities are required and is therefore subadditive. A point such as P that appears below the line would probably be simply additive. A suitable statistical analysis is required to demonstrate the nature of the interaction [15].

In this review paper, an emphasis has been given exclusively on the synergistic effect and mechanism of the various plant based bioactives and treatments of cancer, having least harmful effects. Moreover the conventional treatments for cancer such as radiotherapy, chemotherapy and immunotherapy have been discussed along with their advantages and disadvantages.

Available treatments for cancer:-

Radiotherapy:- Radiotherapy is widely used for treatment of various types of cancer. The exposure to high doses of gamma ionizing radiation (IR) causes severe DNA damages which induces apoptosis of cancer cells. However, it reflects the acquisition of radio-resistance after exposure to sub lethal IR. These sub lethal radiations modulate differentially glioma cell division kinetics [16]. It could cause a shift from asymmetric to symmetric division or a fast cycle of glioma stem cells. Secondly, cancer stem cells are more resistant to radiation than that of cancer cells [17-19]. Resistance of cancer stem cells is caused by their preferential activation of the DNA damage response [20].

Chemotherapy:-

Conventional chemotherapy administration is based on the concept of maximum tolerated dose (MTD) to kill as many tumor cells as possible. Cytotoxic chemotherapy interrupts microtubule formation which is essential for mitotic events that affect cell survival [21]. The current approaches to chemotherapy include the use of alkylating agents, antimetabolites and platinum analogs which also have adverse side effects on normal healthy cells [12]. The side effects include nausea, hair loss, skin irritation, vomiting etc.

Immunotherapy:-

Immunotherapy is a treatment used to kill tumor cells. In this treatment, certain molecules present on the surface of the tumor cells get exposed in order to make them more antigenic or visible to the immune cells. It tends to elicit a stronger immune response that destroys cancer cells but spare healthy tissues. An immunotherapy strategy aims at killing tumor cells directly which involves the injection of cytokines such as tumor necrosis factor (TNF) and interferon (IFN) or interleukin such as IL-2 to force tumor cells to undergo apoptosis or to keep them from replicating [22].

Anticancer efficacy of plant based natural products:-

Natural dietary components are evolutionary-selected molecules which can control inflammation and cancerous transformation and progression. The polyphenols are the natural plant extracts which acts as anti-oxidants and protect the cells against damage caused by free radicals and reactive atoms that contribute to a type of damage in the body. Polyphenols deal with the treatment of various cancers as they break down the action of enzymes that cancers need for the growth and also deactivate substances that promote growth of cancers. The polyphenol most strongly associated with cancer prevention is EGCG [23]. Vegetables, chocolates, cereals and dry legumes also contribute to total polyphenol intake.

Many studies assessed the beneficial properties of key molecules extracted from grapes [24]. Polyphenols found in green tea include catechins, tannins, flavonoids etc. Catechins are the most effective polyphenols that work against UV radiation, photo oxidation, induction of inflammation, oxidative stress and DNA damage from different stress sources etc.

Some polyphenols obtained from plants induce a favorable endothelial response in hypertension and beneficial effects in the management of other metabolic cardiovascular risks [25]. Cocoa contain many different types of physiologically active components. It is proven that cocoa beans are rich in specific antioxidants such as flavonoids, catechins, epicatechins etc. Along with these compounds, beta-sitosterol, the most common phytosterol, may play a protective role in the development of cancer.

Raspberry extract:-

A study on raspberry polyphenols shows that they exhibit anticancer effects on *in vitro* models of colon cancer. There is a probable association between consumption of fruit and vegetables and reduced risk of cancer of the digestive tract. This anticancer activity has been attributed by the anti-oxidant components of this food. Raspberry extract, bioavailable in colon contains phyto-chemicals surviving the digestion procedure that mimicked the physiochemical conditions of the upper gastro intestinal tract [26]. The polyphenol rich extract is assessed for anticancer properties in a series of *in vitro* systems that serve as model for important stages of colon carcinogenesis, initiation and invasion. The phytochemical composition of colon available raspberry extract (CARE) is monitored using liquid chromatography spectroscopy (LCMS). Initiation caused by CARE causes significant protective effects against DNA damage induced by hydrogen peroxide in HT2a colon cancer cells which can be measured using single cell micro electrophoresis. Promotion caused by CARE significantly decreased the population of HT2a cells in the G1 Phase of the cell cycle. However, addition of CARE over a range of concentrations (0 -50 µg/ml GAE) had no significant effect on barrier function of the CACO-2 monolayer. In vitro the raspberry phytochemicals are likely to reach the colon capable of inhibiting several important stages in colon carcinogenesis.

Red wine extract:-

Studies have suggested that moderate red wine consumption has protective effect on colorectal cancer in both men and women. Many polyphenols present in red wines such as quercetin, catechin [27], gallic acid and resveratrol [28] are known to function as potential chemopreventive agents. An inverse relationship between resveratrol and breast cancer risk has been observed [29]. It interferes with the multi-step process of carcinogenesis and inhibits tumor cell cycle as well as induction of tumor cell death.

Achyranthesaspera:-

Polyphenolic compounds of *Achyranthesaspera* (PCA) extracts are also found to be anticancerous and possess cytokine based immunomodulatory effects. PCA extract contains many known components of phenolic acid and flavonoids such as quinic acid, chlorogenic acid, kaempferol, quercetin and chrysin [30]. These compounds target anti-inflammatory genes expression slowing or preventing the oxidative stress, DNA damage and activation of NF-kB and stat3 signaling pathway in cancerous tissues [31]. These activities help in prevention of malignant transformation of lung cells. PCA reverse, suppress, prevent and delay the carcinogenic process by blocking the early development or early lesion or by inhibiting the progression to invasive cancer.

Curcumin:-

Curcumin is another polyphenolic curcuminoid obtained from turmeric rhizome *Curcuma longa* that has antitumor effects. Docetaxel (doc) is the first-line chemotherapy for treatment of lung cancer. Curcumin synergistically enhances the antitumor efficacy of doc against lung cancer. Curcumin has chemopreventive and chemotherapeutic activity influencing various aspects, such as cell cycle arrest, differentiation and apoptosis in a series of cancer [32,

33]. In addition, curcumin also delays uterine leiomyosarcoma cells growth through protein kinase B-mammalian target of rapamycin pathway and promotes cell apoptosis to suppress malignant pleural mesothelioma growth [34, 35].

Synergy of anticancer compounds:-

Epicatechin (EC) and Epicatechingallate (ECG):-

Melanoma is the leading cause of skin cancer related deaths. The effects of green tea polyphenols (GTPs), a natural mixture of monomers, on melanoma cancer cell growth have been investigated [36]. Epicatechin is the important class of polyphenols under which epigallocatechin (EGC), EGCG and other polyphenols are categorized. A study has reported that tumor necrosis factor- α (TNF- α) releases a protein that demethylates the cancer cells from further division. EGCG is reported to inhibit DNA methyl transferase activity that leads to reactivation of epigenetically silenced genes in cancer cells [37]. Synergic effects are seen when EC and epicatechingallate (ECG) but not with EGC. With the recent advances in the field of epigenetics, studies have indicated that unsilencing of tumour suppressor genes in cancer cells involves changes both in the methylation status of DNA and in the neighboring histone code. For example, in adenomatous polyposis coli (APC) mutant mice treated with sulforaphane, an isothiocyanate from broccoli, there was inhibition and suppression of initial polyps. Mice were given EGCG alone and a combination of EGCG and sulforaphane but no synergistic effects were found.

Thearubigin (TR) and Genistein (GS):-

Normally when the polyphenols are obtained from the plants, the proteins and other components are separated by LCMS and other methods. But when the polyphenols are directly supplied through diet without any separation, they oxidize into compounds like thearubigin (TR) and genistein. Cell cycle analysis has been reported using these compounds [38]. Different cell lines are tested using varying combined ratios of TR < EGCG and genistein [38]. The results indicate a low dose of TR and genistein at a ratio of 1:40 is optimal. Differences in cell growth have also been found. Increased cell growth has been reported when TR alone was used while combination of TR and GS succeeded to reduce cell numbers showing synergistic effect.

Grapes extract and green tea extracts:-

The grape extract interacts, often synergistically, with decaffeinated green tea extracts both in the inhibition of ENOX activity and in the inhibition of cancer cell growth. Intra tumoral injections of 25:1 mixture of green tea extracts and ground frozen dried pomace is nearly as effective as standard synergistic green tea capsicum mixtures in inhibiting growth of UT1 mammary tumors [39]. Grape extracts are rich in several bio-flavonoids including resveratrol and quercetin, both of which retards tumor growth, NF-kappa B activation, cytokine synthesis and cyclooxygenase (COX) expression.

The tNOX, tumour specific growth proteins, are present on the cell surface and are responsible for increase in size of cell following cell division. The polyphenols used are mainly targeted on tNOX. They bind to tNOX and block them from further division, thus causing apoptosis. At therapeutic doses, such substances slow the growth of cancer cells and inhibit tNOX but have no effect on growth of non-cancer cells which shows the potential anticancer activity of grapes and grape extracts [40].

Deguelin and cisplatin:-

One of the most common cancers is the gastric cancer which is usually treated by chemotherapy, radiation and surgeries. Platinum based drugs are extensively used for cancer that decreases the proliferation of cancer cells. But this treatment is costly and also leads to some side effects as it has potential toxicity. Alternatively polyphenols such as deguelin and cisplatin, show the decrease in the proliferating activity of the cancer cells. Deguelin and cisplatin are the natural rotenoids isolated from several plant species. Deguelin has anti-tumor activity and chemo preventive activity whereas cisplatin has proliferation mechanism [41]. The combination of deguelin and cisplatin has been found to increase therapeutic efficiency of each drug resulting in a synergistic interaction.

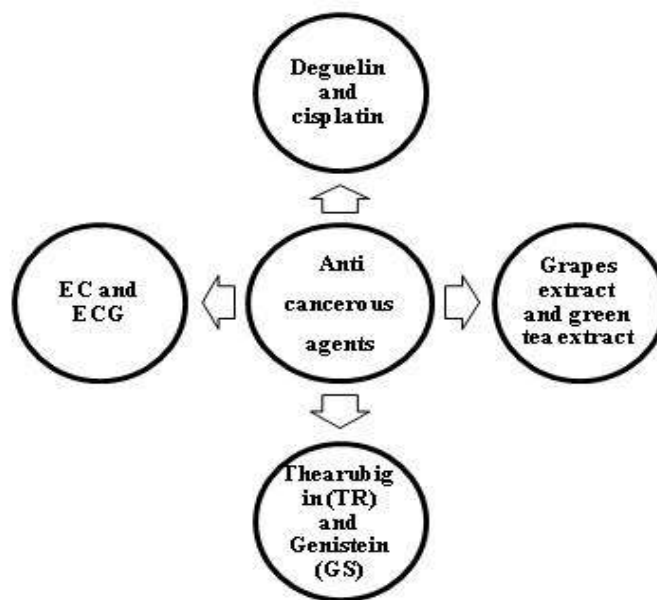


Figure 2:- The figure shows the combination of various natural/plant based bioactives showing synergistic effect against cancer.

Conclusion:-

Polyphenols and other plant based bioactives can be used as an alternative to available synthetic drugs and treatments. The synergistic interaction shown by the combination of various plant based bioactives can be used to increase their individual efficiency against cancer. However, combination of a synthetic drug along with a polyphenol/plant based bioactive may prove beneficial and more effective in the treatment of cancer as well. Chemotherapy, used in cancer treatment, also harms the normal cells of the body along with the cancerous cells due to the oxidative stress produced by it. Hence the synergistic activity of a synthetic drug and polyphenols/other plant based bioactive can show anti-oxidative activity, reducing the side effects of these available treatments. Thus, natural therapies may decrease the cancer rate worldwide and their use over synthetic drugs is more advantageous as they have fewer side effects. Hence, there is a wide range of scope for polyphenols and other plant based bioactives as a novel alternative to the available preventive and therapeutic measures for cancer.

References:-

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J cancer*. 2015; 136.
2. Bilimoria KY, Winchester DP. The importance of worldwide Cancer Registration. *J SurgOncol*. 2008; 97:481-2.
3. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. eds. Cancer incidence in five continents. Vol. VII. Lyon IARC Sci Publ. 1997; 648.
4. Levi F. Cancer incidence in five continents, Vol. VI. *Eur J Cancer*. 1994; 29A:2315-9.
5. IARC Working Group. Handbook of Cancer Prevention, Vol. 7. Lyon France: IARC Press, 2002.
6. Stewart B, Kleigues PE. World Cancer Report. Lyon France: IARC Press, 2003.
7. La Vecchia C, Bosetti C, Lucchini F, et al. Cancer mortality in Europe, 2000- 2004, and an overview of trends since 1995. *Ann Oncol*. 2010; 21:1323- 60.
8. Curado MP, Edwards B, Shin HR, et al. Cancer incidence in Five Continents. IARC Sci Publ. No. 160. Lyon: IARC. 2007. 9.
9. Rodriguez-Vida A, Chowdhury S. Diagnosis and management of testicular cancers. *Trends in Urology & Men's Health*. 2013; 4:25-30.
10. Ferlay J, Soerjomataram I, Ervik M, et al., GLOBOCAN 2012 v1.0. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon France: IARC. 2013.
11. Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol* 2002; 146:1- 6.

12. Fernando W, Rupasinghe HP, Hoskin DW. Regulation of Hypoxia-inducible Factor-1 α and Vascular Endothelial Growth Factor Signaling by Plant Flavonoids. *Mini Rev Med Chem*. 2015; 15:479-89.
13. Müller J, Pfaffl MW. Synergetic down regulation of 67 kD Alamine receptor by the green tea (*Camellia sinensis*) secondary plant compound epigallocatechingallate: a new gateway in metastasis prevention? *BMC Complement Altern Med*. 2012; 12:258.
14. Chou TC. Theoretical Basis, Experimental Design, and Computerized Simulation of Synergism and Antagonism in Drug Combination Studies. *Pharmacol Rev*. 2006; 58:3621-81.
15. Tallarida RJ. Drug Synergism: Its Detection and Applications. *J PharmacolExpTher*. 2001; 298:865-72.
16. Gao X, McDonald JT, Hlatky L, Enderling H. Acute and fractionated irradiation differentially modulate glioma stem cell division kinetics. *Cancer Res*. 2013; 73:1481-90.
17. Pajonk F, Vlashi E, McBride WH. Radiation resistance of cancer stem cells: the 4 R's of radiobiology revisited. *Stem cells*. 2010; 28:639-48.
18. Kim MJ, Kim RK, Yoon CH, et al. Importance of PKC δ signaling in fractionated-radiation-induced expansion of glioma-initiating cells and resistance to cancer treatment. *J Cell Sci*. 2011; 124:3084-94.
19. Rycaj K, Tang DG. Cancer stem cells and radioresistance. *Int J Radiat Biol*. 2014; 90:615-21.
20. Bao S, Wu Q, McLendon RE, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature*. 2006; 444:756.
21. Marchetti P, Urien S, Cappellini GA, Ronzino G, Ficarella C. Weekly administration of paclitaxel: theoretical and clinical basis. *Crit Reviews OncolHematol*. 2002; 44:3-13.
22. Rescigno M, Avogadri F, Curigliano G. Challenges and prospects of immunotherapy as cancer treatment. *BiochimBiophysActa*. 2007; 1776:108-23.
23. Chen D, Wan SB, Yang H, et al. EGCG, green tea polyphenols and their synthetic analogs and prodrugs for human cancer prevention and treatment. *AdvClin Chem*. 2011; 53:155-77.
24. Signorelli P, Fabiani C, Brizzolari A, et al. Natural grape extracts regulate colon cancer cells malignancy. *Nutr Cancer* 2015; 67:494-503.
25. Fernández-Arroyo S, Camps J, Menendez JA, Joven J. Managing Hypertension by Polyphenols. *Planta Med*. 2015; 81:624-9.
26. Coates EM, Popa G, Gill CI, et al. Colon available raspberry polyphenols exhibit anticancer effects on in vitro models of colon cancer. *J Carcinog*. 2007; 6:4.
27. Ebeler SE, Breneman CA, Kim GS, et al. Dietary catechin delays tumor onset in a transgenic mouse model. *Am J ClinNutr*. 2002; 76:865-872.
28. Angel-Morales G, Noratto G, Mertens-Talcott S. Red wine polyphenolics reduce the expression of inflammation markers in human colon-derived CCD-18Co myofibroblast cells: potential role of microRNA-126. *Food Funct*. 2012; 3:745-752.
29. Levi F, Pasche C, Lucchini F, Ghidoni R, Ferraroni M, La Vecchia C. Resveratrol and breast cancer risk. *Eur. J. Cancer Prev*. 2005; 14:139-142.
30. Narayan C, Kumar A. Identification and characterization of phenolic compounds in hydro methanolic extract of *Achyranthesaspera* (HMEA) by UPLC and MALDI-TOF-MS and in vivo antioxidant activity. *Orient Pharm Exp Med*. 2013; 13:51-9.
31. Narayan C, Kumar A. Constitutive over expression of IL-1 β , IL-6, NF- κ B, and Stat3 is a potential cause of lung tumorigenesis in urethane (ethyl carbamate) induced Balb/c mice. *J Carcinog*. 2012; 11.
32. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res*. 2003; 23:363-98.
33. Duvoix A, Blasius R, Delhalle S, et al. Chemopreventive and therapeutic effects of curcumin. *Cancer Lett*. 2005; 223:181-90.
34. Wong TF, Takeda T, Li B, et al. Curcumin disrupts uterine leiomyosarcoma cells through AKT-mTOR pathway inhibition. *GynecolOncol*. 2011; 122:141-148.
35. Wang Y, Rishi AK, Wu W, et al. Curcumin suppresses growth of mesothelioma cells in vitro and in vivo, in part, by stimulating apoptosis. *Mol. cell. Biochem*. 2011; 357:83.
36. Prasad R, Katiyar SK. Polyphenols from green tea inhibit the growth of melanoma cells through inhibition of class I histone deacetylases and induction of DNA damage. *Genes Cancer* 2015; 6:49-61.
37. Dashwood RH. Frontiers in Polyphenols and Cancer Prevention. *J. Nutr*. 2007; 137:1 267S-9S.
38. Sakamoto K. Synergistic effects of thearubigin and genistein on human prostate tumor cell (PC-3) growth via cell cycle arrest. *Cancer Lett*. 2000; 151:103-9.
39. Morré DM, Morré DJ. Anticancer activity of grape and grape skin extracts alone and combined with green tea infusions. *Cancer Lett*. 2006; 238:202-209.

40. Sedlak D, Morré DM, Morré DJ. A drug-unresponsive and protease-resistant CNOX protein from human sera. Arch. Biochem. Biophys. 2001; 386:106-116.
41. Li Z, Wu C, Wu J, et al. Synergistic antitumor effects of combined deguelin and cisplatin treatment in gastric cancer cells. OncolLett. 2014; 8:1603-7.