Phenolic Compounds from Plants -An Important Class of Phytomedicine in Wrestle against Cancer-A Review

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Abstract

Phenolic and Polyphenolic are important compounds from the class of phytomedicine and are widely distributed in the plant kingdom. Over the years, an increasing amount of interest has been vastly drawn into the plant polyphenolic mainly because these compounds have shown tremendous efficacy in the treatment of oxidative stress-related diseases such as cancer. Currently, much medical investigations are conducted on plant phenolic for improving their identification and development for better therapeutic efficacy in the fight against different types of cancers. We aim to update and provide an extensive overview of the mechanism of action and the role of phenolic compounds in the treatment of tumor. The various databases used to conduct the literature survey are (Pub Med Central, Scopus, Research Gate, EMBASE, Google Scholar, Science Direct, Sci ELO, PLoS (Public Library of Science). In the first stage it includes different types of cancers and their biomarkers. In second stage, different phenolic compounds in plants and their role in the cancer treatment. Finally, to find out the mechanism of action and clinical status of phenolic compounds against different biomarkers and the mechanism of action of phenolic and polyphenolic compounds against cancer and its biomarkers with their antioxidant activity.

Index terms— plant phenolic; antioxidant; anticancer; pro-oxidant.

1 Introduction

he term cancer is related to uncontrolled growth of abnormal cells in which the immune system fails to control these cells that leads to uncontrollable multiplication and spreadability to different parts of the body. [1] Despite the advancements in the diagnosis and treatment of cancer, [2] the mortality rate by cancer has been progressively increasing worldwide. [3] In 2018, the mortality by different cancers such as; Lung (1.76 million), Colorectal (8,62,000 deaths), Stomach (7,83,000), Liver (782,000 deaths), Breast (627,000 deaths). The number of deaths (9.6 million), new cases of cancers (17 million) in which male population (8.8 million) and female population (8.2 million) reported in 2018. It is expected that new cases will increase up to 27.5 million by 2040 representing 61.7% increment from 2018. [5] [6] II.

2 Cancer and Types of Cancer

Melanoma skin cancer develops from the melanocytes usually on the chest and back part of the body. Basal cell and squamous cell cancers are the most predominant skin cancers and not spread to other parts of the body. [6] [7] The oral cavity cancer develops in the mouth, while oropharyngeal cancer begins in the oropharynx. They develop from squamous cell carcinomas, verrucous, minor salivary gland carcinoma, and lymphoma. [7] Lung cancer develops in lung tissues, especially in the air passages of cells lining and further categorized into non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), Mesothelioma. [8] [9] Gastric cancer is triggered by Helicobacter Pylori, dietary patterns, socioeconomic status, genetic predisposition, environmental factors. [10] Colon and Rectal cancer are known as single tumor entity; hence, it is called colorectal cancer. Colorectal cancer involves the cancer formation in the colon, rectum and in the appendix. [11] [12] Kidney cancer

is abnormal kidney cell growth and further categorized into renal cell carcinoma, transitional cell carcinoma, nephroblastoma. [13] Urinary Bladder Cancer is the uncontrolled growth of the cells of bladder and without treatment cancer cells can spread to other tissues of the body. Bladder cancer includes urothelial carcinoma (transitional cell carcinoma), squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. [13] [14] Leukemia is part of the heterogeneous group of cancers linked with the hematopoietic system and characterized by uncontrolled proliferation of leukocytes in bone marrow. It is divided into lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). [15] [16] T Ovarian cancer is not necessarily from ovarian but can originate from the fallopian tube. There are various types of ovarian cancers such as epithelial ovarian tumors, ovarian germ cell tumors, and ovarian stromal tumors. [17] [18] III.

3 Different Cancer Biomarkers

Biomarkers are biological molecules present in blood, tissues, lymph and they serve as a signaling agent for normal or abnormal functioning of the body. Biomarkers include proteins, nucleic acid, antibodies, peptides and others that give the indication of disease due to alteration in the germline or somatic mutations, transcriptional and post-translational alteration and also changes like in gene expression, metabolic and proteomic changes can also serve as biomarkers. [19] Biomarkers can be classified based on disease state (prediction biomarkers, detection biomarkers, diagnostic biomarkers, prognosis biomarkers), based on biomolecules (DNA biomarkers, RNA biomarkers, protein biomarkers, and based on other criteria (imaging biomarkers, pathological biomarkers, in-silico biomarkers). [20] Cancer biomarkers can further be categorized into the following classes: a) Prognostic biomarkers Prognostic biomarkers which help in predicting the cancer and its nature course that differentiate between good and poor tumor outcome as well as how strong the treatment is to be done, [21] Predictive markers provide upfront information about the possible success or failure of a specific treatment, [22] Pharmacodynamic markers provide information on the effectiveness of the drugs on the body which incorporate the drug effect on the target cancer cell and also provide the effect of the body towards the drug including the absorption, distribution, metabolism and elimination of the drug. These markers are also important in the dose optimization which does not reach to the cytotoxic levels, diagnosis biomarkers are very important due to the fact that they are probably present in the early stages of cancer which include calcitonin in medullary thyroid cancer. [20]

4 b) Ovarian cancer biomarkers

Various biomarkers are currently being used in the efficient detection of ovarian cancer as shown in (Fig. **??**), and new generation of biomarkers for ovarian cancer is under clinical trial. **??**23] [24] Fig. **??**: Schematic representation of different biomarkers used in the detection of ovarian cancer. Breast cancer type 1 susceptibility protein (BRCA1), Carbohydrate antigen 125 (CA 125), Human epididymis protein 4 (HE4), HE4 + CA125, Prostasin + CA 125, Kallikrein-related Peptidase 6 (KLK6) (hK6), KLK6 + CA 125, B7-H4, B7-H4 + CA 125, Osteopontin biomarker which help in prediction of ovarian cancer.

5 c) Acute myeloid leukemia biomarker

Various biomarkers are currently being used in the efficient detection of ovarian cancer as shown in (Fig. **??**). **??**25] [26] Fig. **??**: Schematic representation of different biomarkers used in the detection of acute myeloid leukemia. MLL-AML, Promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) markers for diagnosis and monitoring of acute myeloid leukemia.

6 d) Biomarkers in urinary bladder cancer

For the detection of bladder cancer, various biomarkers have been used as shown in Fig. 3). **??**27] [28] Phenolic Compounds from Plants -An Important Class of Phytomedicine in Wrestle against Cancer-A Review

7 e) Biomarkers in colorectal cancer

The following markers (Fig. **??**) are used in the detection of colorectal cancer. **??**29] [30] [31] [32] Fig. **??**: Schematic representation of different biomarkers used in the detection of colorectal cancer. POLE (DNA polymerase epsilon) and POLD1 (DNA polymerase delta 1) mutations, DNA MMR genes/MSI, EGFR/HER family, TP53-APC/?-catenin, KRAS (Kristen rat sarcoma virus), Carcinoembryonic Antigen (CEA), Epidermal growth factor receptor (EGFR).

8 f) Biomarkers for detection of lung cancer

For the detection of lung cancer, various biomarkers are used as shown in Fig. 5 [30] [9] [33] [34] Urinary Bladder Cancer

9 g) Biomarkers in pancreatic cancer

The following (Fig. 6) represent genetic biomarkers used in pancreatic cancer detection along with (tissues biomarkers). [35]

10 h) Biomarkers in cervical cancer

The following biomarkers are used for detection of cervical cancer (Fig. **??**). [24] Fig. **??**: Schematic representation of different biomarkers used in the detection of cervical cancer. Squamous cell carcinoma antigen, CEA, CA 125, and cytokeratins (TPA, tissue polypeptide specific antigen-TPS, CYFRA 21-1).

11 i) Biomarkers in breast cancer

For the detection of breast cancer the following biomarkers are used (Fig. 8). [36] Phenolic Compounds from Plants -An Important Class of Phytomedicine in Wrestle against Cancer-A Review IV.

28 Year 2019

12 Phenolic Compounds in the Prevention of Cancer Formation

The factors that can contribute significantly to the formation of cancer include intrinsic risk (random error in DNA replication), extrinsic risk further divided into endogenous risk factors (biological aging, genetic susceptibility, DNA repair mechanism, hormones, growth factors, inflammation) and exogenous risk factors (radiation, chemical carcinogens, tumorcausing viruses, bad lifestyle like smoking, lack of exercise, nutrient). **??**37] [38] Phenolic compounds are well documented for their anticancer properties by reducing intrinsic and extrinsic factors and by interfering with the metabolism of pro-carcinogens by regulating the expression of cytochrome P450 enzymes. Increase the excretion by increasing the expression of conjugating enzymes phase II. Production of toxic quinones which is the substrate of this enzyme in the body, thus, their absorption can stimulate detoxication activity which will result in protection against toxic xenobiotics. Polyphenolic compounds like quercetin, catechins, isoflavones, lignans, Flavanones, red wine polyphenols, resveratrol, and curcumin can stimulate apoptosis of tumor cells and inhibit angiogenesis; thus reducing the growth of tumor. [39] The increasing threat from the free radicals in current days enhances the importance and use of phenolic compounds. Free radicals can worsen the already existing pathological condition, trigger the onset of action of disease and eventually develop new pathological conditions. Thus, phenolic compounds can play an important role in preventing this disease e.g. cancer, neurodegenerative diseases. Phenolic compounds offer a prominent capacity in providing the oxidative balance in the body by protecting against oxidative reactions, oxidants, and reactive species. Phenolic compounds are chemically different. Thus, they show their action through different polyvalence reactions, by enhancing the potential of some compounds, blocking the side effects of other compounds and presenting other biological activities used as antibacterial, anticancer, anti-inflammatory, diabetes, hypertension, obesity, Alzheimer. [40] Many components from plants are subjected to an exhaustive study on their antioxidant properties. [41] The importance of plants is vastly used in the treatment and prevention of cancer. [42] Antioxidants act by complexing metal ions, scavenging of free radicals, and the decomposition of peroxides. Most of the anticancer drugs available today about 60% derived from the plant source. **??**43] [44] Phenolic is made up of aromatic ring which is made up of one or more hydroxyl group, and it is present in many flowering plants, vegetative organs, in flowers and many fruits, cereals, seeds. [45] The phenolic hydroxyl group, however, is influenced by the presence of the aromatic ring. Due to this aromatic ring, the hydrogen of the phenolic hydroxyl is labile, which makes phenols weak acids. [46] These compounds action is not solely owned by their antioxidant effects but also antiviral, immune-stimulant, antibacterial, estrogenic effects, cytotoxic properties in various tumor cells. [47] Plant phenols are grouped into simple and complex phenolic acids. Simple phenolic acids are divided into benzoic acid and cinnamic acid. The complex phenolic acid is divided into three classes (Tannins, Flavonoids, and Stilbenes). [48] Phenolic compounds have been classified into different groups as described below in Fig. 9. V.

13 Mechanism of Action of Various Phenolic Compounds in Cancer Development

Phenolic compounds have shown cancer prevention ability in the different type of cancers.

14 a) Activity of phenolic compounds against prostate cancer

Delphinidin has the ability to inhibit cell growth and promote caspase-mediated apoptosis which leads to tumor size reduction, this was observed by in-vitro human cell lines and in-vivo murine models assay, 7-hydroxymatairesinol which can inhibit tumor growth and stop tumor cell proliferation this was observed by in-vivo murine assay, Caffeic acid through LNCap cell lines assay have shown the ability to inhibit tumor cells growth, Ferulic acid by PC-3 cell lines assay have presented inhibitory effect on tumor size ultimately leading to apoptosis. [49] b) Activity of phenolic compounds against leukemia cancer Delphinidin-3-sambubioside can lead to inhibition of Caspase-3,-8 and 9 ultimately leading to apoptosis activation which was observed by in-vitro human cell lines assay, Podophyllotoxin and polyethylene by in-vitro human cell lines have shown better tumor inhibition as compared to podophyllotoxin alone, [50] Podophyllotoxin and fatty acids analogs possess cytotoxic effects towards cancer cells and low toxicity towards sane cells, this was seen by in-vitro human cell lines assay. [51] c) Activities of phenolic compounds against lung cancer Cyaniding-3-rutinoside and cyaniding-3glucoside by in-vitro human cell lines assay have shown dose-dependent tumor inhibitory effect, p-coumaric acid by A549 assay have present tumor inhibitory activity, Quercetin in PEG 400 liposomes possess Tumor inhibition activity which

leads to apoptosis has seen in in-vivo murine models assay. [52] d) Activity of phenolic compounds against gastric cancer Cyanidin-3-0-glucoside through in-vivo human cell lines assay demonstrated a decrease in cell proliferation and morphological changes which ultimately lead to apoptosis. [53]

15 e) Activity of phenolic compounds against skin cancer

Ferulic acid through in-vivo murine cells assay have shown the ability to prevent the tumor formation, Kraft lignins by in-vitro human cell lines and in-vivo murine cell lines assay have shown Adsorption to nitrosamines DNA protective effect against tumor, Resveratrol have shown inhibition of pre-neoplastic lesions and tumorigenesis inhibition has seen in in-vivo murine xenografts assay. [54]

16 f) Activity of phenolic compounds against colon cancer

Cinnamic acid through HT-29 cell line assay have shown inhibition of tumor growth, p-coumaric acid through SW-620 cell line assay has shown inhibition of tumor size growth. [55] g) Activity of phenolic compounds against breast cancer Gallic acid can lead to tumor size reduction has seen in MDA-MB-231 cell line assay, Caffeic acid can cause inhibition of tumor growth, and apoptosis demonstrated by MDA-HB-231 assay. [56]

17 h) Activity of phenolic compounds against bladder cancer

Dicoumarol can lead to enhancement of the anticancer effect of the drug which is shown by in-vitro human cell line assay. [57] i) Activity of phenolic compounds against renal cell cancer Daphnetin with the help of in-vitro human cell line assay has shown activation of P 38 cell cycle arrest, coumarin through epidemiological studies assay has shown enhancement of the anticancer effect of various drugs used in renal carcinoma. [58] Due to the difference in the structures and molecular targets the anticancer activity differs among the various phenolic compounds. Antioxidant and in-vitro anticancer activities of phenolics isolated from sugar beet molasses. Phenolic compounds that possess a greater number of hydroxylic groups show better anticancer activity in comparison with -OCH 3 moieties. [59] Plant polyphenols has shown therapeutic effects as antioxidants and free radicals scavengers not only against cancer but also against pro-oxidation, anti-diabetic, LDL oxidation, antibacterial, antiviral, anti-inflammatory, anti-allergic, lipid-lowering, and anti-aging. [60] Cancer development is divided into various stages for example initiation, promotion, progression, invasion, and metastasis. The mechanism of action of phenolic compounds in various stages of cancer progression is described in Fig. **??**0. [61] Fig. **??**0: Mechanism of action of phenolic compounds in tumor development.

Phenolic compounds plays different role against oxidation pathways and free radicals, oncogenic pathway, tumor suppression pathway, cytokine cell differentiation pathway, matrix metalloproteinases, Cyclin-dependent Kinases (CDKs) and Anaphasepromoting enzymatic complex (APC/C), p53, Bcl-2 markers, estrogen receptors (ER's), HER2 markers, TPA and DMBA markers against cancer. [62] VI. Phenolic Role against Oxidation Pathways and free Radicals

Oxidative stress means lack in the balance between oxidant by-products and the antioxidant defense system which is directly associated with metabolism and the antioxidant defense mechanism. [63] Enzymes like catalase, superoxide dismutase, and glutathione peroxidase constitute the antioxidant defense system. [64] In some disease condition or in depletion of antioxidant these controls the mechanism is not sufficient and oxidant by-products which can lead to DNA damage protein and lipids. [65] Mitochondria, phagocytic cells, peroxisome fatty acid, and certain enzymes are responsible for the production of oxidant by-products in cells. Exposure to cigarette smoke, excessive iron and copper intake by diet can as well lead to oxidative stress. Superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, chain reaction mechanism in lipids and nitric oxide radicals outstand as the most important oxidative by-product of cells. **??**65] [66] The chain reaction mechanism can be classified into the following steps: ? Initiation step (where the free radicals are formed); ? Propagation step (where free radicals converted into other radicals); ? Termination step (where two radicals combine with the formation of stable products).Initiation: ROOHâ??"ROO?+H ROOHâ??"RO?+OH- 2ROOHâ??"RO?+H2O+ROO? Propagation R?+O2â??"ROO? ROO?+RHâ??"ROOH+R? Termination ROO?+ROOâ??"ROOR+O 2 RO?+Râ??"ROR

Phenolic compounds often referred to polyphenols are compounds with one or more aromatic ring(s) having hydroxyl substituent(s), and obtained from the plant secondary metabolite. The antioxidant activity varies depending on the structure of the compound. Flavonoids stand as the most prominent antioxidant compound as compared to others because they scavenge reactive oxygen species and nitrogen-reactive species in a much faster rate. They also scavenge superoxide, hydroxyl, peroxy radicals, peroxynitrous acid, and hypochlorous acid. Despite the tremendous advantages of phenolic compounds as an antioxidant agent, only a certain number of phenolic compounds have been approved for used in formulations and food products due to the risk of toxicity or carcinogenic effect. [67] Degenerative diseases like arteriosclerosis and cancer are the result of free radicals and lipid peroxidation. A successful antioxidant activity of a phenolic compound against lipid oxidation is associated with the free radical scavenging activity of the phenolic compound. [68] The action of phenolic compounds in scavenging free radicals is due to their structure base on the fact that phenolic hydroxyl groups are prone to donate a hydrogen atom or an electron to a free radical. Also, because extended conjugated aromatic system to delocalize an unpaired electron. e.g., Resveratrol, a phenolic compound acts as an antioxidant found in grapes,

red wine, peanuts, chocolate, certain berries, and possess a strong antioxidant effect, having large number of health benefits in various studies. [66] OH HO OH

18 Resveratrol a) Phenolic role against the oncogenic pathway

The oncogene is the result of mutations in the proto-oncogenes. This mutation allows oncogenes to make protein coding which allows cancer cells to proliferate and survive in the different environment. There is no need for the mutant B-Raf to translocate and associate with Ras protein to show enzymatic activity. [69] Thus, this results in uncontrolled proliferation of cancer cells which results in malignant metastatic tumor formation. [70] Various compounds have demonstrated their capacity in inhibiting cancer proliferation, for example caffeic acid inhibited metastasis of cancer in the colon. In the same way protocatechuic acid inhibited NF-K? and MAPK does control the proliferation of lung and gastric carcinoma cells. Ferulic acid and caffeic acid phenyl ester have shown down regulation of phosphorylated P13K and AKT which inhibited melanoma cells proliferation as well as induced apoptosis. [71] OH O HO

19 HO

20 Caffeic acid

21 COOH OH OH

22 Ferulic acid b) Phenolic role against tumor suppression pathway

The function of a tumor-suppression gene is to protect the normal cells or healthy cells by preventing oncogenic transformation into cancer or unhealthy cells. The example of tumor suppressors includes p53, PTEN, Rb proteins which prevent DNA damage caused by dyes, high-intensity radiation. [72] Despite this action, tumor suppressors also help in scavenging the damaged cells through the process of apoptosis. Resveratrol, a stilbene compound can also increase the expression of p53 in cervical cancer and inhibit the growth of ME180 cells. **??**73] [74] c) Phenolic role against cytokine and cell differentiation pathways Interferons, interleukins, tumor necrosis factor, lymphokines are known as cytokines and are involved in cell signaling, development, and immune responses. The release of these cytokines in uncontrolled fashion will result in either oxidative stress or chronic inflammation, thus malignancy in the normal cells. [75] Myc-c is the gene that regulates 70% of cancers. The mutation of Myc-c will result in unsuccessful control of differentiation of cells. Myc-c is actively involved in cell cycle regulation metabolism, differentiation, and cell growth. Thus, the phenolic compounds for example curcumin that can inhibit cytokines proliferation are important anticancer agents.

23 Curcumin d) Phenolic role against matrix metalloproteinases enzyme

Cancerous cells exhibit high degradation of extracellular matrix of a healthy cell to promote tumor invasion and metastasis; this is the characteristic of matrix metalloproteinase which are endopeptidase. Molecules like protocatechuic acid, ferulic acid are capable of inhibit MMP and can also stop growth of tumor cells. [77] The derivatives of cinnamic acid for example CAA and CAPE can inhibit MMP-9 and MMP-2 activities, thus prevent hepatoma cells growth and metastasis. Hence, phenolic derivatives with MMP inhibition characteristics can prevent metastatic spreading of cancerous cells. [78] HO HO O

24 OH

25 Protocatechuic acid e) Phenolic role against Cyclin-dependent Kinases (CDKs) and Anaphase-promoting enzymatic complex (APC/C)

The regulation of CDK complexes is the result of binding of p21 and p27 with CDK, thus, the cell cycle activity is controlled due to the polyphenolic modulating activity on cyclins, APC/C or CDK. [79] In colon cancer polyphenolic compounds have shown cell-cycle arrest activity in S and G2/M phases and HCT-116 cells. The decrease in cyclin A and D1 levels by polyphenolic compounds for example red grape wine polyphenol, phenolic acids, flavonoids, carotenes causes cell-cycle arrest in MCF-7 cells in breast cancer. [80] O In various functions associated with cellular stress, cell proliferation, and death the tumor suppressor p53 is activated. Several researches have shown that plant phenolic and extracts possess the ability to activate p53 or p53 mediated pathway. In the first approach demonstrated that plant phenolic like taxifolin and quercetin possess the ability to disrupt interactions between Mdm2 and p53, thus, the degradation of p53 is completely prevented. [81] O HO The use of polyphenolic compounds for example Ellagic acid (EA) can decrease the expression of Bcl-2 in breast cancer and increase p21 levels by phosphatidylinositol-3, 4, 5-triphosphate-3-phosphatase which lead to

tumor apoptosis. [80] The effect of polyphenolic compound on estrogen is mainly due to the similar structure of flavonoids, isoflavones, Lignans and estrogen. Epigallocatechin gallate (EGCG) participates in the regulation of ER by down regulating the ER-? protein, gene promoter and mRNA actions in MCF-7 and ER. [80] i) Polyphenolic role against Human epidermal growth factor receptor 2 (HER2) HER2 can spread by homo-or hetero-dimerize in addition with other HER upon its activation by activating P13K/AKT and Ras/MAPK. Polyphenolic compounds for example extra-virgin olive oil polyphenols, lignans can decrease HER2 activation or they can inhibit HER2 expression. The blocking of HER2 occurs by preventing ATP to bind with tyrosine kinase, suppression activity on pathways of HER2/HER3-PI3K/AKT, and another mechanism also includes the inhibition of binding between HER2-Hsp90. [80] OO O O O R 2 O R 3 R 1 O H 3 CO HO O OCH 3 OH OH O O OCH 3 OH OCH 3 HO H 3 CO OCH 3

26 Olive oil Lariciresinol (LAR) Syringaresinol (SYR) j) Polyphenolic compounds role against TPA and DMBA markers

The promoter of 12-O-tetradecanoyl phorbol-13-acetate (TPA) is inhibited by phenolic compounds which include protection against UVB light and induce apoptosis. Polyphenols for example polyphenol of green tea tannins, curcumin, phenolic acid, polyphenols in black tea and green tea can inhibit 7, 12-dimethyl benzene (a) anthracene (DMBA) even after the process was already initiated and TPA promotion has taken place. [81] Polyphenols can inhibit the cellular signaling in NF-kB, thus, results in apoptosis by the activation of DNA-PK-p53. [82] The inhibition DMBA/TPA-induced skin cancer can result in the inhibition of the skin tumor by blocking the inflammation promoter which includes interleukins which decreased Ha CaT cells by blocking the pathways of MAPK. The inhibition of 13 cis-retinoic acid also contributes in inhibition of skin tumor. [83]

27 Flavonoids Role in Cancer

They are polyphenols with 15 carbon atoms, two aromatic rings bound through a three carbon chain (C6-C3-C6) which can eventually be part of a third ring. The chemical diversity of these compounds derived from this carbon skeleton. These compounds can exist in free or conjugated forms in nature esterified to one or two sugar molecules through one hydroxyl group (O-glucosides, O-Gluc). [85] They inhibit the formation of reactive species by chelating the metal ion, for example, iron and copper. Flavonoids can also present bio-molecular damage by peroxynitrite in vitro, inhibit activation of the carcinogenic metabolite, cell-cycle arrest through apoptosis, and prevent proliferation and angiogenesis. Apigenin, it stops the cell adhesion and invasion, decreases diolepoxide 2 formations, inhibits mitochondrial proton F0F1-AT Pase/ ATP, inhibits prostaglandin and IL-6, 8 production, prevents expression of intercellular adhesion molecule-1 (ICAM-1). Genistein, luteolin, quercetin, and silymarin, has shown antimutagenic and antiangiogenesis activities. Sylimarine can inhibit apoptosis and inhibit protein kinases whith MAPK. [86] Quercetin anticancer activity is the result of its action on caspases-3 inhibition, lymphocyte tyrosine kinase inhibition, telomerase inhibition, protein kinase inhibition and its effect on increasing the expression of quinine oxide reductase, nicotinamide adenine dinucleotide phosphate. Daidzein, hesperetin, Kaempferol, and myrcetin have presented anti-inflammatory characteristics. [87] [88]

28 c) Lignans activity on cancer

These are dimmers having two C 6 -C 3 units from the tail-to-tail linkage of two conifers. Example of this compound includes Sesamol and its glucoside. [89] Lignans have presented antimutagenic activity regulation of enzyme expression, antiangiogenic activity which can result in cell-cycle arrest and apoptosis in breast cancer. Sesamin has shown an effect on leukemia, breast and stomach cancer by acting as an antioxidant, triggering apoptosis and cell-cycle arrest. [90] OO O O O O H H

29 Sesamin d) Coumarins activity on cancer

Coumarins along with 7-hydroxycoumarin can inhibit cell proliferation and stop cell-cycle; thus, result in apoptosis. Esculetin (6, 7-hydroxycoumarin) can inhibit lipoxygenase and prevent the proliferation. [91] O O HO HO Casuarinin inhibit progression of the cell cycle in G0/G1 which results in apoptosis in breast cancer. [74] e) Phenolic acids activity on cancer It counts for about 30% of dietary polyphenols and second most abundant in the polyphenolic family. Phenolic compounds have been divided into various classes, for example, Hydroxycinnamic acid including caffeic acid, ferulic acid and also into Hydroxybenzoic acid, for instance, gallic acid. [92] All these compounds have shown efficacy as an anticancer and antimetastatic agent as well as effects on mesenchymal characteristics of cancerous cells. [93] [94] [95] Various phenolic drugs are obtained from the botanical source and few of these drugs.

30 O OH OH OH HO

31 Gallic acid f) Quinones activity on cancer

These are phenolic antioxidants obtained naturally. Purpurin, and alizarin were the most effective quinones. Emodin, chrysazine, rhein, chrysophanol, and aloe-emodin were also active but with less great extent due to the absence of ortho-dihydroxy structure. While catechol structure in various phenolic compounds and ortho-dihydroxy structure in hydroxyanthraquinone enhances the scavenging properties of phenolic molecules, on the other hand, glycosylation decreases the scavenging effects of hydroxyanthraquinone. [96] Emodin can inhibit cell-cycle and cause apoptosis by inhibiting casein kinase 2 and urease, inhibit DNA binding, thus blocking the signal transduction pathways. [97] O

32 Safety of Phenolic Plant Compounds

Phenolic compounds are generally safe when ingested directly from plant material. Their consumption from food supplements or herbal medicines can cause systemic toxicity. **??**48] [98] When ingested naturally the body develops mechanisms by which its bioavailability is reduced to avoid toxicity. However, for the pathological treatment, the dose bioavailable must be ensured to avoid failed treatment. On the other hand, the high dose concentration must be limited because it can increase the progress of cancer instead of suppressing it. **??**90] [99] IX.

33 The Adverse Effect of Phenolic Compounds

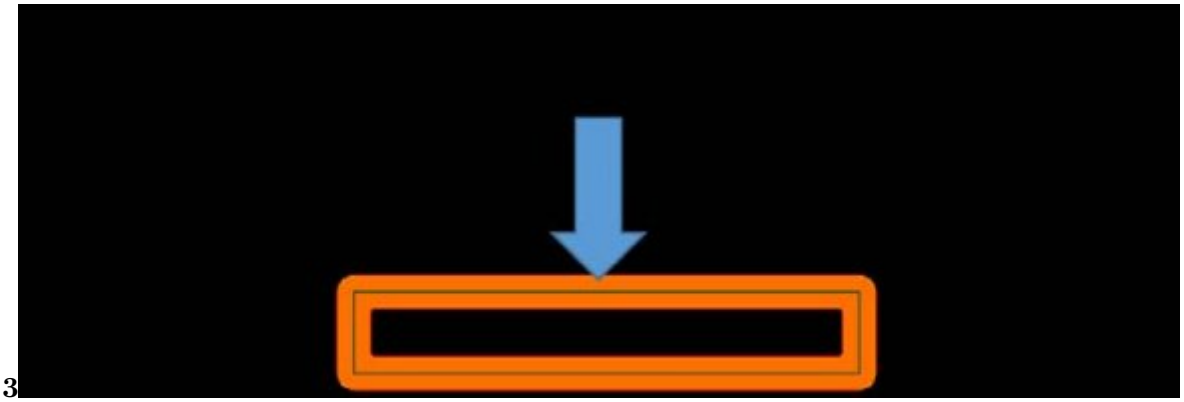
The adverse effects caused by phenolic compounds are mainly because of the following reasons:

? Poor permeability while present as free acids;

? The ability of transforming a healthy cell into cancer cell; ? When given in higher doses it cases toxicity; ? It can lead to infection and unusual inflammatory reaction due to scavenging of reactive oxygen species which is important in many biological processes. **??**100] X.

34 Conclusion

Polyphenolic compounds effect on cancers partly due to their effect on various tumors pathway, for instance, epithelial mesenchymal transition (EMT) pathway, apoptosis induction, ROS levels increase. Nevertheless, the successful efficacy of phenolic and polyphenolic compounds also partly due to their modulation of the immune system and other mechanisms in the body. Phenolic compounds play an important role in tumor pathways and are responsible for mediating cancer cell migration and invasive properties which can justify their polyphenolic compounds also play an important role by up-regulating epithelial markers and down-regulating mesenchymal proteins and their antimetastatic effect. Although phenolic compounds possess extensive benefits to health, it is important to mention that they also possess extensive interaction with other ingested drugs and other food materials. They are subjected to vast metabolic degradation. Hence, it is advisable to always use polyphenolic in synergistic mixture because they exert a more and better therapeutic effect when used in a mixture.



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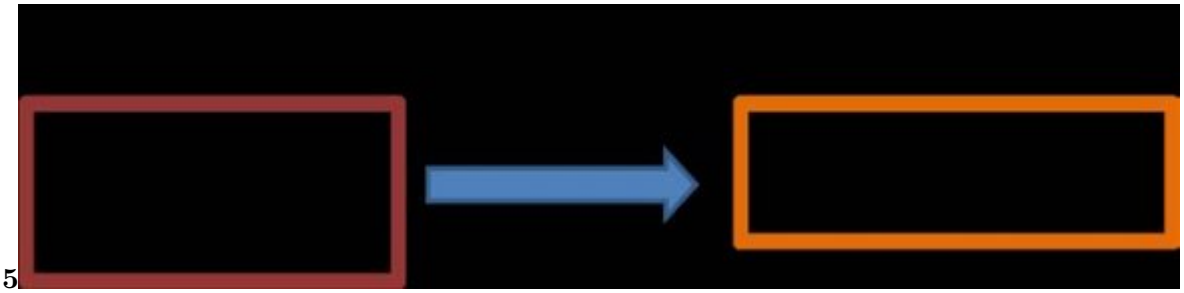

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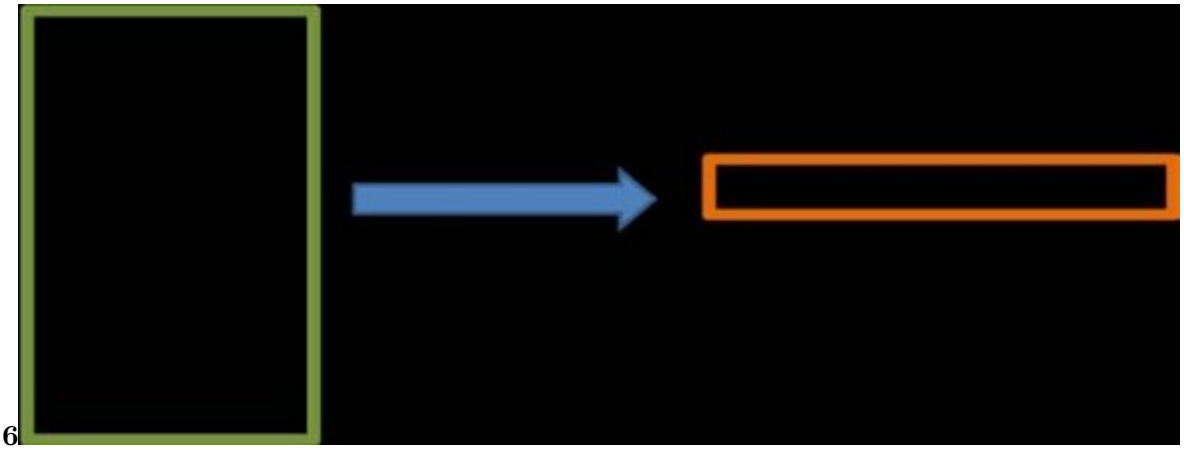

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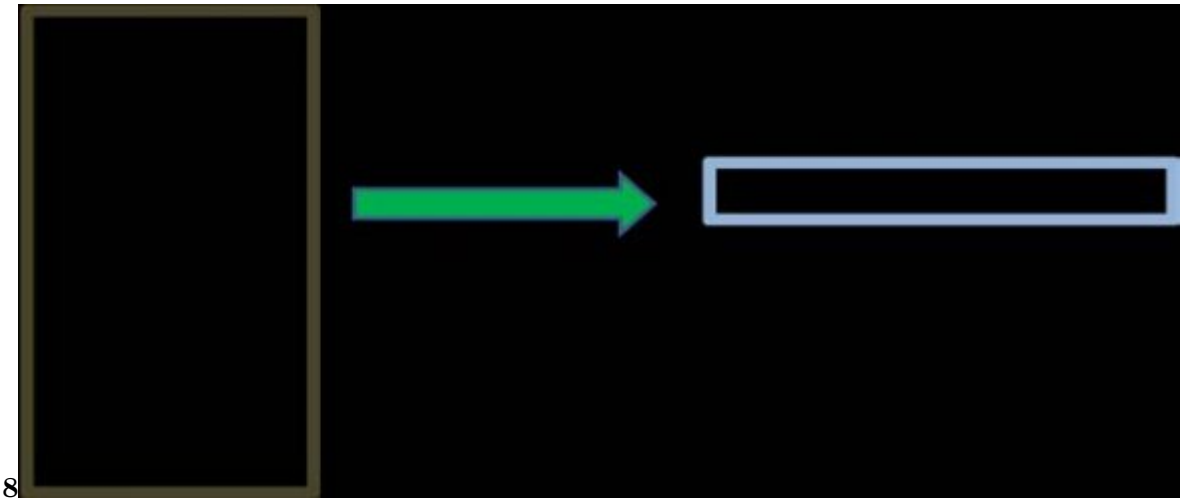

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Figure 4: Fig. 8 :

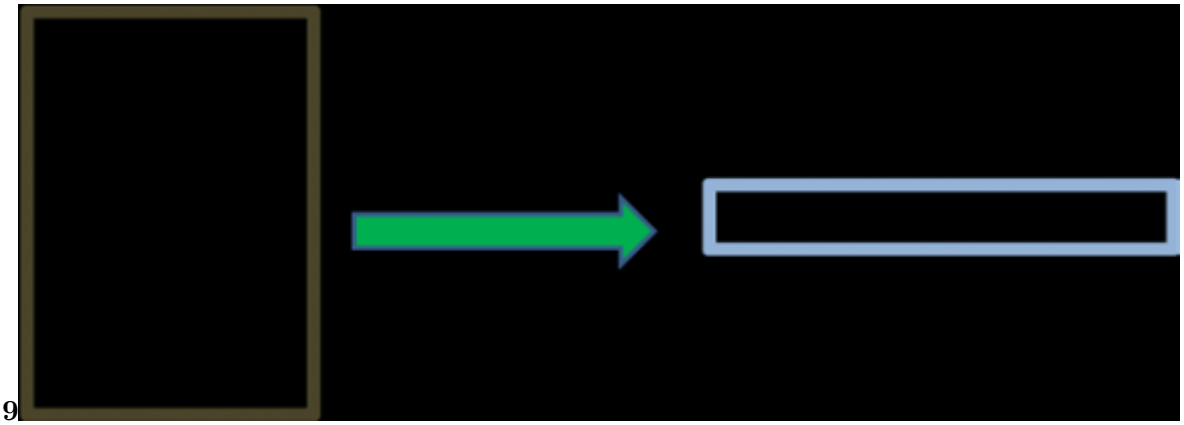

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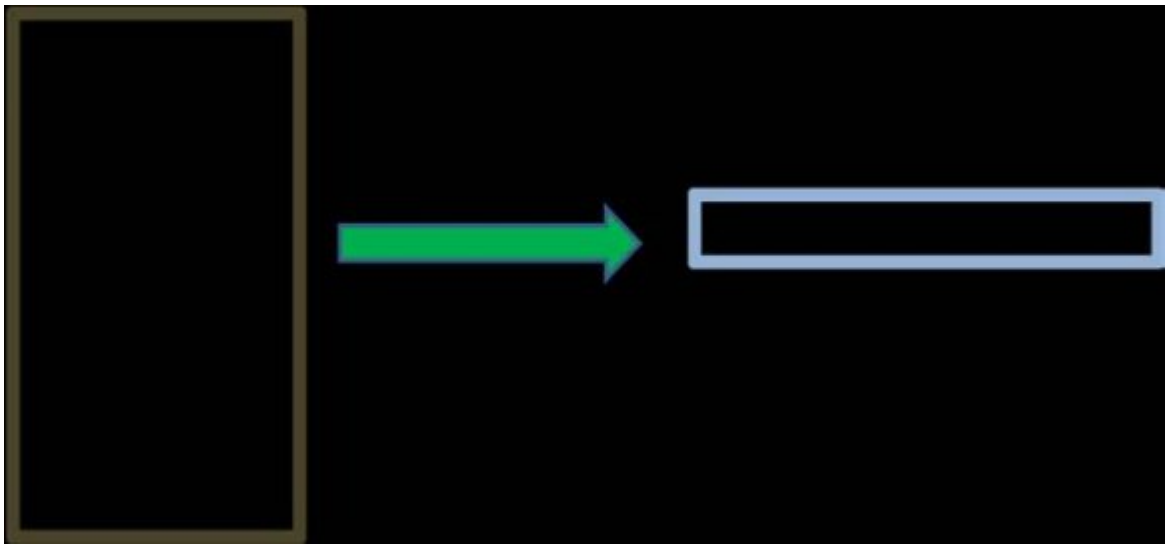
Figure 5: Fig. 9 :



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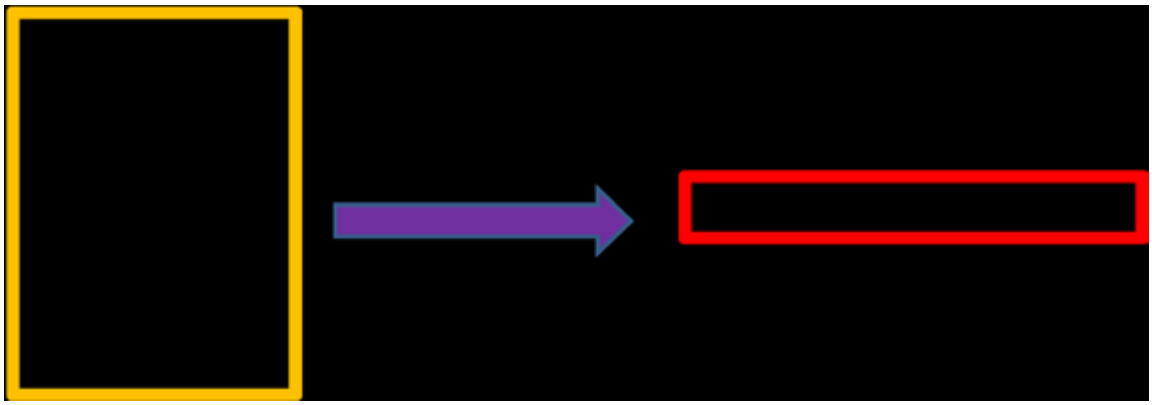


Figure 7:

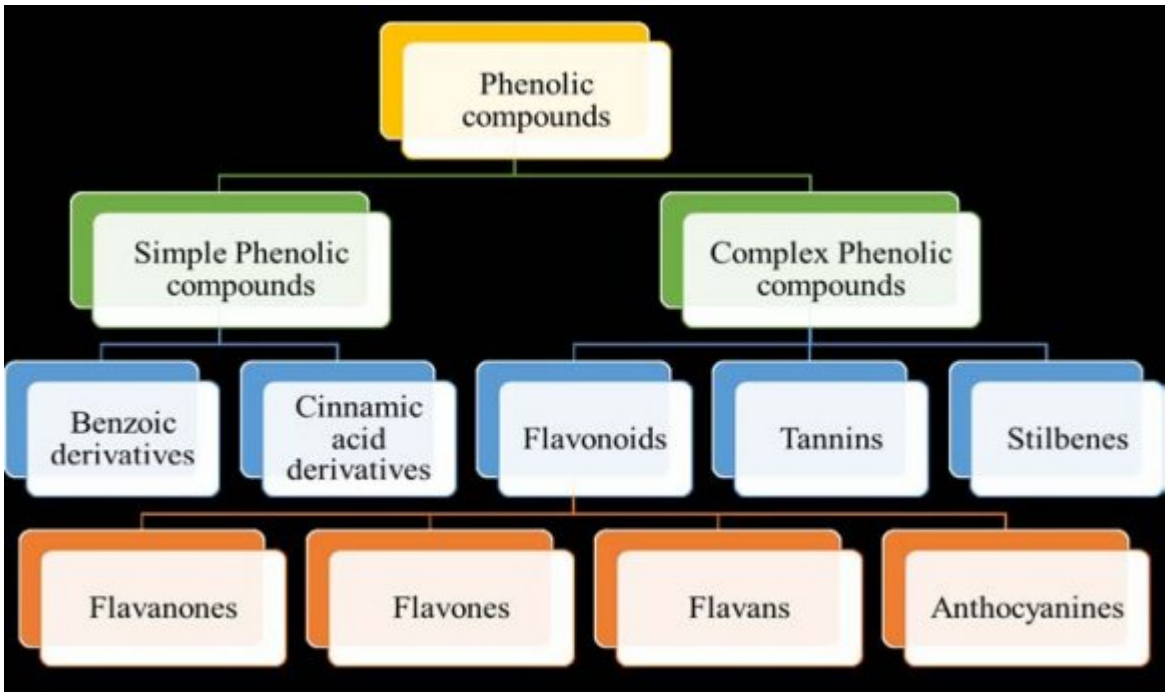
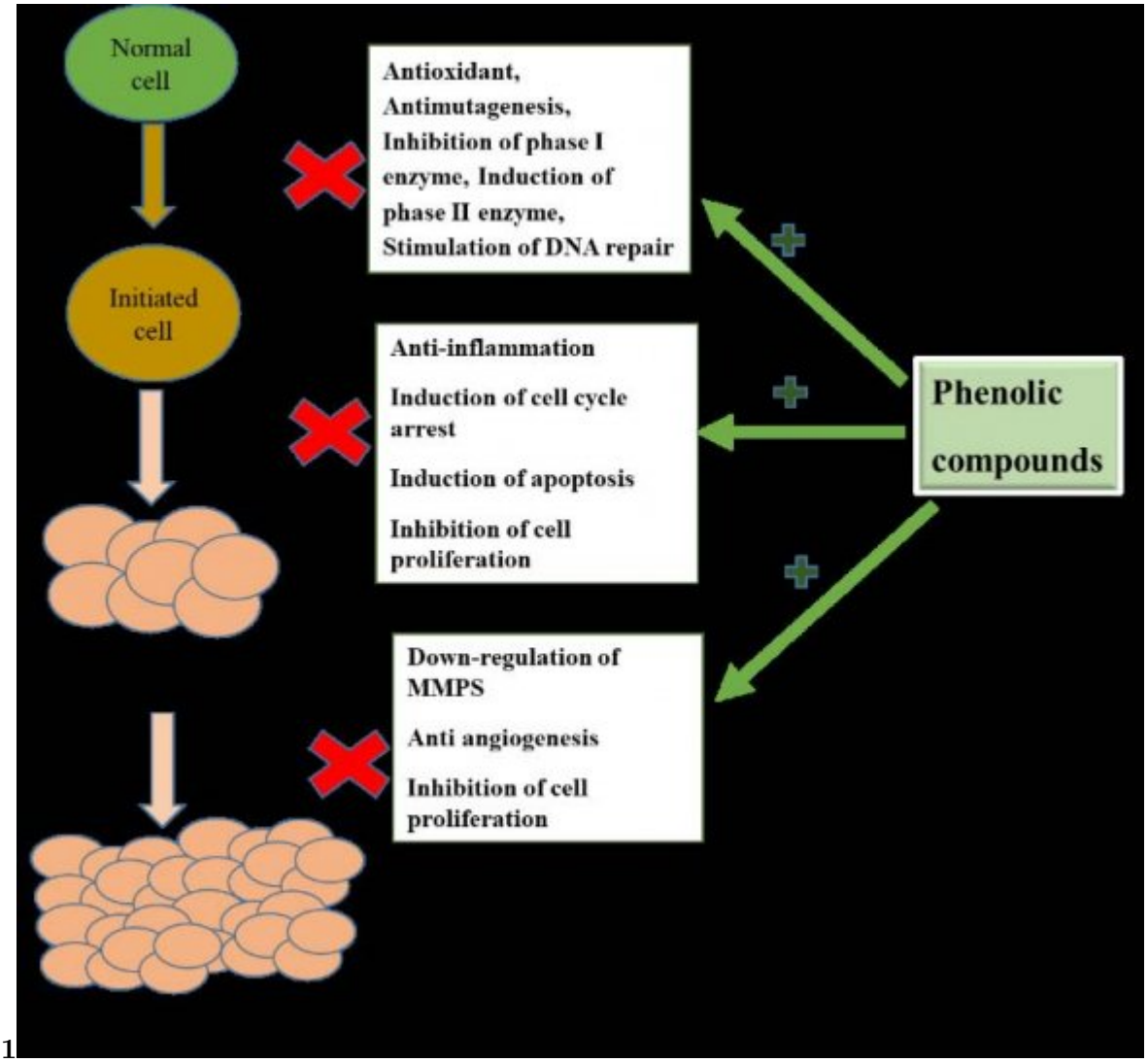

Phenolic compounds
Simple Phenolic compounds
Complex Phenolic compounds
Benzoic derivatives
Cinnamic acid derivatives
Flavonoids
Tannins
Stilbenes
Flavanones
Flavones
Flavans
Anthocyanines

Figure 8:



11

Figure 9: Fig. 11 :

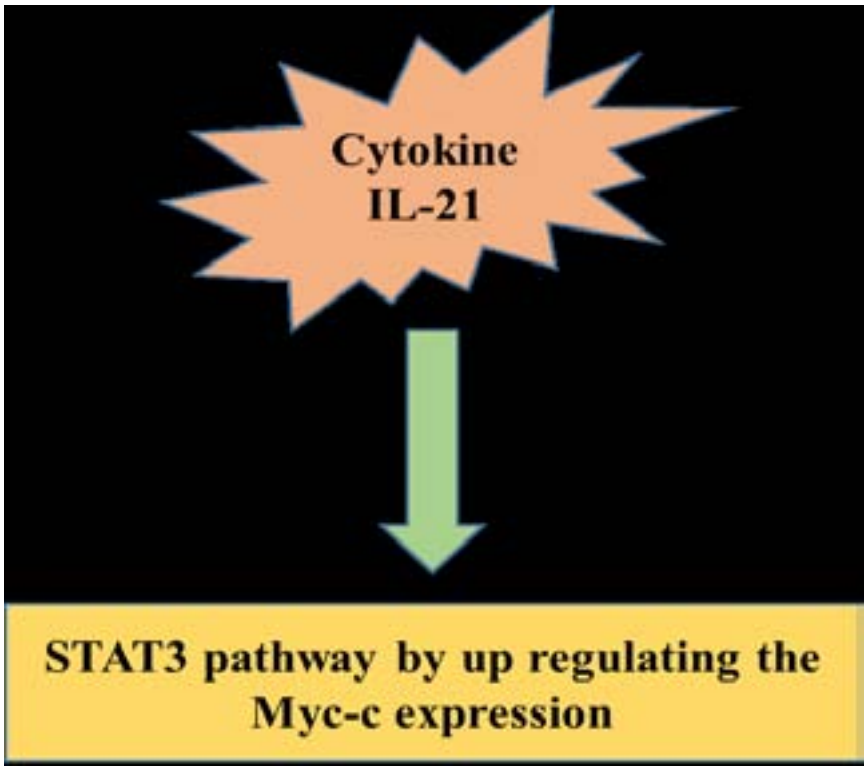


Figure 10:

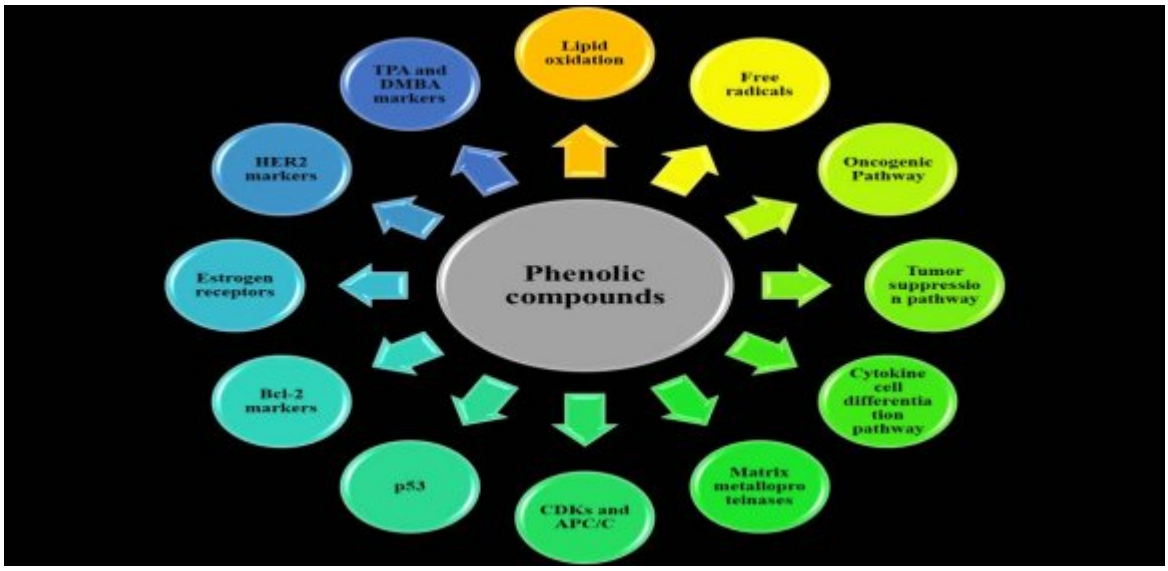


Figure 11:

Figure 12: FGFR3, HRAS, KRAS, NRAS and PIK 3CA mutation,BCL2, CDKN2A and NID2, APC, GSTP1, CDKN2, RASSF1A Aurora-A, serime/threonine kinase, hTERT, SENP1, PPP1CA, and nicotinamide N-methyltransferase (NNMT), Nuclear matrix protein 22 (nmp-22), Bladder tumor antigen (BTA) High molecular CEA and Mucin miRNA, miR-15A, miR-210, miR-378,miR-451, miR-508- 3P, miR-1233, miR-221

1

O Purpurin OH OH O OH OH OH OH

H 3 C O
Emodin

Phenolic Compound	Caffeic acid	Folic acid	Quercetin	Ginseng	Luteolin	Epigallocatechin gallate	Type of C
Ginseng							Non-small
							Breast an
Tannic acid							Metastati
Hesperidin							Breast ca
Tannic acid							
Anthocyanidin							

The list was obtained from https://clinicaltrials.gov

Figure 13: Table 1 :

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[Pan] , *Pan*

[Chai] , H Chai .

[Gougoulias and Papachatzis] , N Gougoulias , A Papachatzis .

[Daniela] , Alesiani Daniela .

[Pichichero] , Elena Pichichero .

[Silva] , JulianaGaspar , Alan E Silva .

[Alves Monteiro] , Jackeline Alves Monteiro .

[Ozcan; A. Akpinar-Bayizit] , T Ozcan; A. Akpinar-Bayizit .

[Gomes] , Catarina A Gomes .

[Gira Da] , Teresa Gira Da , Cruz .

[Preethi et al.] , G Preethi , C Anantharaju; Prathima , Gowda .

[Chen] , M Chen .

[Meng] , H Meng .

[Dai] , Jin Dai .

[Beer] , D Beer .

[Maqsood] , Sajid Maqsood . (Soottawat Benjakul)

[Leicht] , D T Leicht .

[Balan] , V Balan .

[Wajapeyee] , N Wajapeyee .

[Pramanik] , K Pramanik .

[Kudugunti] , S Kudugunti .

[Guo and Ngo] , X E; Guo , B Ngo .

[Yang] , G Yang .

[Jiang] , J Jiang .

[Davies] , H Davies .

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