

**Review Article****Role of different polyphenols in the treatment of cancer disease****Dwaipayan Sinha\****Department of Botany,**Government General Degree College, Mohanpur, Paschim Medinipur, West Bengal-721436, India*

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**Abstract**

Cancer is basically uncontrolled proliferation of cells with altered genetic constituents accompanied by migration from one part of the body to another due to loss of their binding ability and interconnectivity. It has already become a global health problem and the occurrence is increasing day by day with urbanisation and changes in dietary patterns constituting the main reason of its occurrence in addition to genetic causes. The aim of this review is to highlight the pharmacological activity of polyphenols against cancers through an in-depth literature survey. Plants contain a number of bioactive compounds amongst which polyphenols constitute a substantial proportion. They act as strong antioxidants which possibly accounts for its pharmacological activities. Presently, there is a constant effort to explore the anticancer activity of polyphenols isolated from plants. This review discusses the current status of some frequently occurring cancers and summarises the pharmacological activity of selected polyphenols in counteracting the disease. The mechanism of action of polyphenols in counteracting cancer cells have also been discussed in the review. Extensive literature survey has been made to compile relevant information with PubMed forming the search platform. The review highlights the anticancer activity of selected polyphenols. It is evident that polyphenols inhibit cancers largely by counteracting those cellular processes which inhibits the growth, migration and proliferation of cells. Polyphenols can thus become a potent therapeutic agent for treatment of cancer and requires trials on humans satisfying scientific and ethical formalities.

**Keywords:** Cancer, metastasis, proliferation, inflammation, antioxidant, flavonoids

**Introduction**

Cancer is presently becoming a major concern of public health all throughout the globe. Presently cancer is the leading cause of death and forms the most important barrier to an increased life expectancy throughout the globe and accounts for significant proportion of death worldwide (Bray et al., 2018). The incidence of cancer is rapidly growing throughout the world and the major reasons are chemical or environmental exposures due to unplanned industrialization, urbanization and changes in life style. In United States, an estimate of 1735350 new cancer cases and 609640 cancers related deaths have been reported for the 2018 (Siegel et al., 2018). In Europe, 3.91 million new cancer cases and 1.93 million cancer related deaths have been reported in 2018 (Ferlay et al., 2018). The condition of cancer seems to be

more alarming in Asian continent as it accounts for more than half of the total population of the world and the incidence of cancer cases is projected to increase from 6.1 million in 2008 to 10.6 million by the year 2030 (Sankaranarayanan et al., 2014). Reports from Africa states that in the year 2012, there are 850000 new cancer with 600000 mortality due to malignancies cases (Stefan, 2015).

Cancer has caused a high burden worldwide and the primary aim of research to combat cancer now centres on modifying diet and nutrition which can significantly alter and impact the risk of occurrence. Some nutritional exposure such as consumption of alcohol (Mons et al., 2018) and processed meat (Benarba, 2018) are responsible for onset of cancers. There are also reports that excess adiposity in the body which is an outcome of obesity is linked to occurrence of cancers (Sung et al., 2019). Thus one of the important approaches to reduce cancer occurrence is creating a suitable nutritional state and avoiding excess adiposity through consumption of healthy plant foods with comparatively low quantity of meat, avoidance of alcohol, salt preserved food and increasing physical activity (Wiseman, 2018).

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Plant based diets are associated with lowering overall mortality, reduction of medication needs, efficient management of body weight, reduction in incidence of high risk condition such as obesity, obesity related inflammatory markers, hyperglycaemia, hyperlipidaemia and hypertension (Hever and Cronise, 2017). Plant based food broadly comprise dietary fibres and phytonutrients. Dietary fibres comprise of a large group of naturally occurring plant derived carbohydrate polymers and oligomers, resistant to hydrolysis by enzymes of small intestine, with considerable variation in physical and chemical properties, and potent physiological properties (Poutanen et al., 2018). Phytonutrients are compounds produced by the plant involving a wide array of biochemical pathways and include carotenoids, limonoids, phytoestrogens, phytosterols, anthocyanins, probiotics, omega-3-fatty acids and polyphenols. They acts as antioxidants and exhibits specific biological activities benefitting human health and include polyphenols, and omega-3 fatty acids. Over last few years, research on polyphenols has gained tremendous importance due to their beneficial effect on human health. Recent studies indicate that intake of polyphenols results in a reduction in cancers (Grosso et al., 2017). Though they confer their health benefits through a number of mechanistic ways, but it is their antioxidant activity that has been most elaborately explored (Gross et al., 2018).

### What are polyphenols?

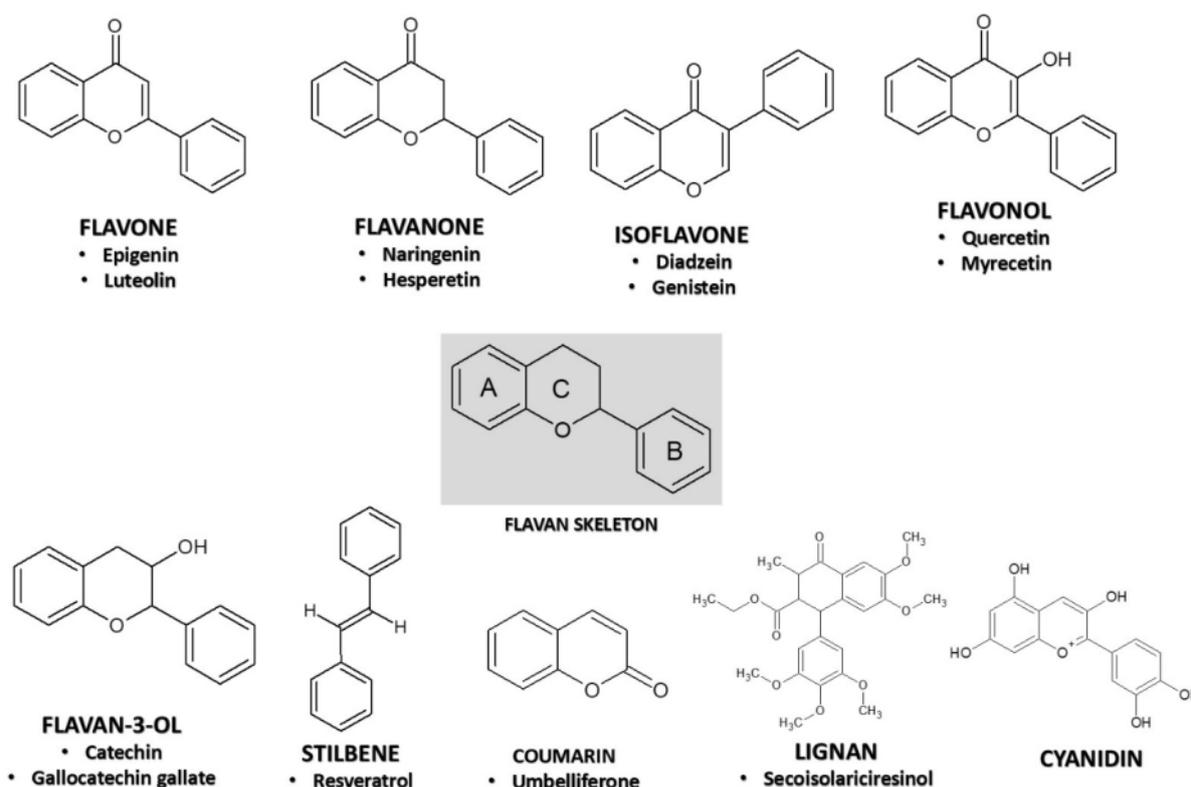
Polyphenols secondary metabolites of plant origin with

phenylalanine or tyrosine acting as a precursor molecule during the biosynthetic process. This involves a deamination process to form cinnamic acids which enters the phenyl propanoid pathway. During this process, one or more hydroxyl groups are attached to the phenyl ring. The C<sub>6</sub>-C<sub>3</sub> phenyl propanoid unit constitutes the fundamental carbon skeleton building unit of all polyphenols. The biosynthetic process then diversifies to a number of pathways generating a large number of polyphenol variants namely benzoic acids (C<sub>6</sub>-C<sub>1</sub>), cinnamic acids (C<sub>6</sub>-C<sub>3</sub>), flavonoids (C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>), proanthocyanidins [(C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>)<sub>n</sub>], coumarins (C<sub>6</sub>-C<sub>3</sub>), stilbenes (C<sub>6</sub>-C<sub>2</sub>-C<sub>6</sub>), lignans (C<sub>6</sub>-C<sub>3</sub>-C<sub>3</sub>-C<sub>6</sub>) and lignins [(C<sub>6</sub>-C<sub>3</sub>)<sub>n</sub>] (Pereira et al., 2009).

Polyphenols may be classified are generally classified depending on the number of phenol rings present in their molecule and the structural elements that attach these rings to one another. The different groups are as follows:

**a) Phenolic Acids:** These molecules consist of a single aromatic ring with a carboxylic acid side chain of one to three carbons. They are of two types namely (i) derivatives of benzoic acid (C<sub>6</sub>-C<sub>1</sub>) and (ii) derivatives of Cinnamic Acid (C<sub>6</sub>-C<sub>3</sub>).

**b) Flavonoids:** The molecule contains a flavan nucleus of 15 carbon atoms arranged in the form of a pair of aromatic rings (A and B), bound together by an oxygenated heterocyclic



**Figure 1.** Molecular skeleton of different flavonoids and the fundamental flavan skeleton showing A, B and C rings (inset).

C-ring. They are further classified into 6 subgroups on the basis of the type of heterocycle involved namely flavanols, flavonols, flavones, flavanones, isoflavones and anthocyanins.

- c) Lignans: The structure consists of a pair of phenylpropane units.
- d) Stilbenes: The structure is based on 1,2-diphenyl ethylene.
- e) Coumarins: The structure is composed of benzo-2-pyrone.
- f) Tannins: They are of two types namely (i) hydrolysable

tannins and (ii) condensed tannins. Hydrolysable tannins have a central core of glucose or other polyol esterified with gallic acid (Gallotannins) or hexadihydroxydiphenic acid (ellagitannins). Condensed tannins are polymers of flavan-3-ols linked by interflavan carbon bonds (Manach et al., 2004; Sirerol et al., 2016). The basic flavan skeletons and molecular structure of selected polyphenols are depicted in figures 1 and 2 respectively.

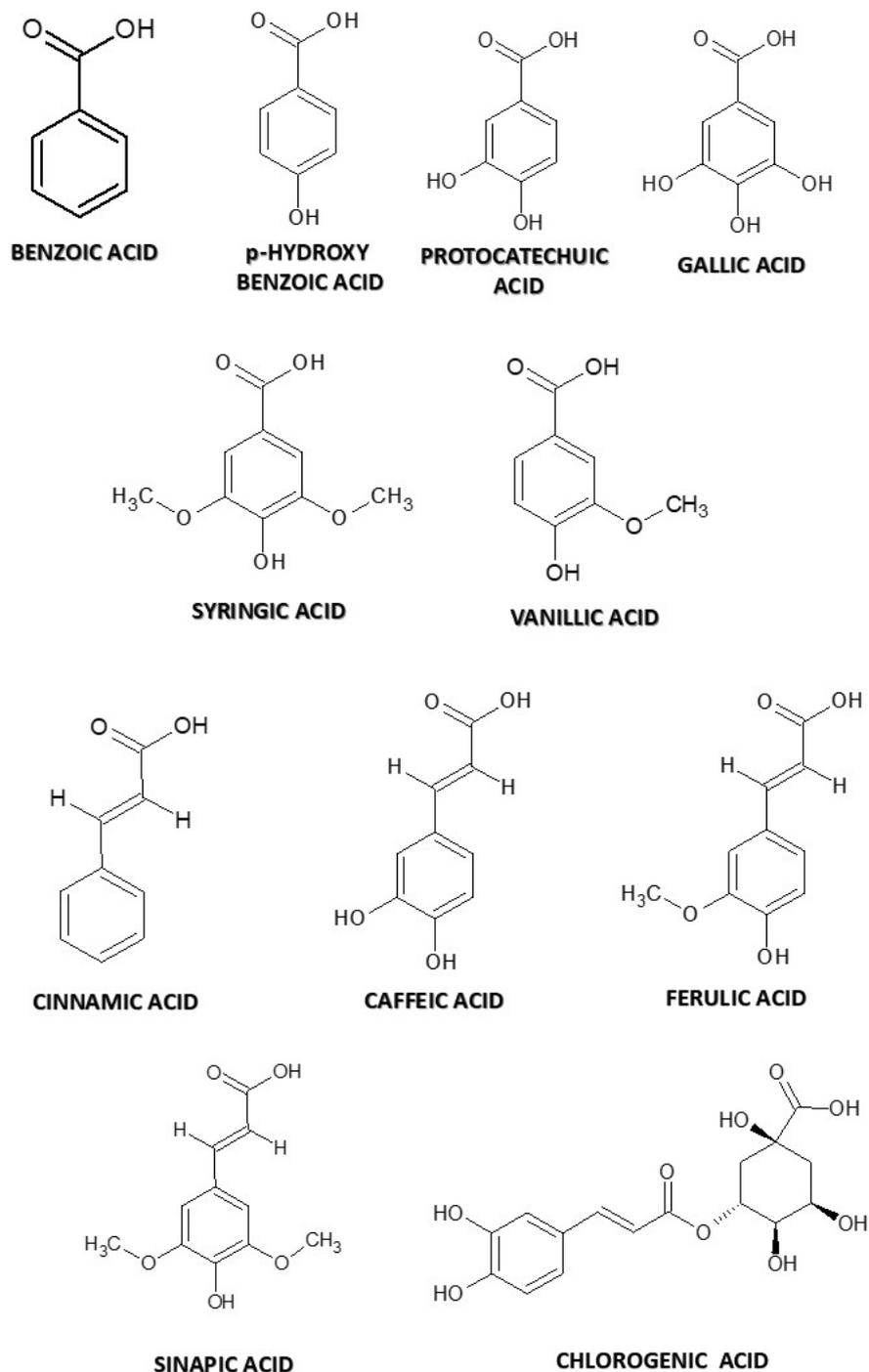


Figure 2. Molecular structure of representatives of Phenolic acids

## Methodology

Extensive literature survey has been made in the internet using PubMed and google as search platforms. The review has been broadly divided into three parts viz: (1) Introduction, (2) current scenario of some cancers selected on the basis of their occurrence among human population and the pharmacological activity of selected polyphenols to counteract the disease and (3) a general discussion about the mechanism of action of polyphenols in counteracting cancer. The first part of the article has been framed with research papers and review articles downloaded from PubMed. The second part of the article deals with the current scenario of some important cancers and the pharmacological activities of selected polyphenols in counteracting cancers. This part was constructed with research papers and review articles from PubMed and with key words such as 'global reports on lung cancer' or 'global scenario of prostate cancer'. The pharmacological activity of the polyphenols in counteracting cancers was also based on PubMed search with 'apigenin and lung cancer' or 'quercetin and breast cancer' as the relevant keywords. The results of pharmacological activity of polyphenols against 12 selected cancers have been tabulated and four relevant papers have been cited to elaborate their anticancer activities with an exception in non-hodgkin lymphoma where two papers have been cited based on relevance and importance. The third part forms the discussion where the mechanism of action of polyphenols has been discussed. Here varied keywords such as 'inhibition of NF- $\kappa$ B by polyphenols' or 'inhibition of akt by polyphenols, molecular docking analysis' have been used depending on the action mechanism and target molecules. In all the three stages, the relevant papers were accessed and incorporated and irrelevant papers were discarded. The second and third sections have been framed selecting research papers or

review articles not more than five years old to the best of feasibility and relevance in order to incorporate as much recent information as possible.

## Current Scenario of selected cancers

### Lung cancer

Worldwide, lung cancer forms the most common malignancy and most common cause of cancer deaths in past few decades (Wong et al., 2017). The number of lung cancer deaths worldwide is expected to grow up to 3 million by the year 2035 and the figures are likely to double both in men (from 1.1 million in 2012 to 2.1 million in 2035) and women (from 0.5 million in 2012 to 0.9 million in 2035) (Didkowska et al., 2016). Outdoor air pollution such as particulate matter, oxides of nitrogen, ozone are considered as possible lung carcinogens (Datzmann et al., 2018). The pharmacological activity of polyphenols against lung cancer is tabulated in table 1.

### Prostate Cancer

Prostate cancer is the second most frequent cancer (after lung cancer) among men and accounts for 1276106 new cases resulting in 358989 (3.8% of all deaths caused by cancer in men) deaths in 2018 (Rawla, 2019). The highest incidence of prostate cancer is Oceania followed by Northern America, Western Europe, Northern Europe, and the Caribbean while the incidence and mortality in African countries have lower incidence rates than that of the developed countries (Taitt, 2018). High Body Mass Index (BMI), smoking habit, consumption of processed red meat, animal fat/ saturated fat are major risk factors of prostate cancer (Peisch et al., 2017). The pharmacological activity of polyphenols against prostate cancer is tabulated in table 2.

**Table 1.** Pharmacological activity of polyphenols against lung cancer

Polyphenols	Experimental system	Important findings	References
Luteolin	<b>Cells:</b> A549 lung cancer cell.	Suppression of antiproliferative activity through induction of apoptosis involving Bcl-2 associated X protein (Bax)/B <sub>2</sub> -cell lymphoma-2 (Bcl-2), caspase and extracellular signal regulated kinase (ERK) / (Mitogen activated protein) MEK signalling pathway.	Meng et al., 2016
Apigenin	<b>Cells:</b> A549 human lung cancer cell.	Inhibition of cancer cell proliferation by targeting Akt and its downstream expression of matrix metalloproteinase 2 (MMP-2), matrix metalloproteinases -9 (MMP-9), glycogen synthase kinase -3 $\beta$ (GSK-3 $\beta$ ), and Human enhancer of filamentation -1 (HEF1).	Meng et al., 2017
Epigallocatechin gallate (EGCG)	<b>Cells:</b> NSCLC, A549, H1299, Lu99 lung cancer cells. <b>Animal:</b> Female A/J mice and C57BL/6 mice.	Inhibition of lung cancer by modulation of Programmed cell death ligand 1 (PDL1) expression and reduction in levels of phosphorylated Signal Transducer and Activator of Transcription 1 (p-STAT1) and p-Akt.	Rawangkan et al., 2018

### Breast cancer

Breast cancer is the most common cancer amongst women and the second most common cancer across the world with a projected figure of 1.7 million new cases by the year 2020 (Rivera-Franco and Leon-Rodriguez, 2019). About 5-10% of the breast cancers are related to inherited mutations in Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) genes (Feng et al., 2018). An important intrinsic factor responsible for occurrence of breast cancer is age. It has been reported that breast cancer is most frequently found in women around menopause and less frequent in women around 45 years of age (Kamińska et al., 2015). Consumption of alcohol (Lammert et al., 2018) and red processed meats, trans fatty acids and foods which results in higher circulating levels of insulin and insulin like growth factors (IGF1) also promote breast cancer (Seiler 2018). The pharmacological activity of polyphenols against breast cancer is tabulated in table 3.

### Colorectal cancer

Colorectal cancer is the third most common cancer worldwide and the fourth most common cause of death with nearly 1.8 million new cases and 881000 deaths in the year 2018 (Araghi et al., 2019). The global colorectal cancer burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by the year 2030 (Colace et al., 2017). Lynch syndrome is one such condition which falls within hereditary colorectal cancer syndrome and is caused by mutation in one of the DNA mismatch-repair genes: mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), PMS2 or epithelial cell adhesion molecule (EPCAM) (Kuipers et al., 2015). Another most common colorectal cancer syndrome is familial adenomatous polyposis, characterized by the presence of hundreds to thousands of polyps in the colon and rectum and occurs due to mutation in adenomatous polyposis coli (APC) gene

**Table 2.** Pharmacological activity of polyphenols against prostate cancer

Polyphenols	Experimental system	Important findings	Reference s
Caffeic Acid	<b>Cells:</b> LNCaP prostate cancer cells. <b>Animal:</b> mice.	Retardation of prostate cancer tumour through induction of cell cycle arrest, decrease in levels of fatty acid synthase (FAS), retinoblastoma protein (Rb), abundance of total Akt, Akt1, Akt2 and regulation of S <sup>2</sup> -phase kinase associated protein 2 (Skp-2), Nuclear Factor- $\kappa$ B (NF- $\kappa$ B) p65 and associated proteins.	Lin et al., 2016
Naringenin	<b>Cells:</b> PC3 and LNCaP prostate cancer cells.	Induction of apoptosis through increased expression of Bax, modulation of Phosphoinositide 3-Kinase (PI3K)/Akt and ERK1/2 pathways.	Lim et al., 2017
Quercetin	<b>Cells:</b> LNCaP, DU-145 and PC-3 prostate cancer cells.	Induction of apoptosis through modulation of apoptotic machinery involving BAX, Bcl-2 like protein 11 (BIM), p53 up regulated modulator of apoptosis (PUMA) and PI3K/Akt pathway.	Ward et al., 2018

**Table 3.** Pharmacological activity of polyphenols against breast cancer

Polyphenols	Experimental system	Important findings	Reference s
Quercetin	Cells: MDA-MB-231 breast cancer cell.	Induction of apoptosis and inhibition of cell cycle progression, induction of p53, promoter activity of p21 and increased activity of Growth arrest DNA damage (GADD45). Activation of Forkhead box O3a (Foxo3a) and c-Jun N-terminal kinases (JNK).	Nguyen et al., 2017
Apigenin	<b>Cells:</b> MDA-MB231 and MDA-MB436 breast cancer cells. <b>Animal:</b> BALB/c nude mice.	Inhibition of breast cancer cells by decreasing yes-associated protein 1 (YAP)/Taffazin (TAZ) activity, levels of Connective tissue growth factor (CTGF) and Cysteine-rich angiogenic inducer 61 (CYR61) and disruption of interaction of TAZ and YAP with transcriptional enhanced associate domain (TEAD).	Li et al., 2018
Quercetin	<b>Cells:</b> MDA-MB-231 and MCF-7 breast cancer cells.	Inhibition of cancer cells by suppressing key glycolytic enzymes namely Pyruvate Kinase M2 (PKM2), Lactate Dehydrogenase A (LDHA), glucose transport protein 1 (GLUT1) and inactivation of Akt-mTOR pathway.	Jia et al., 2018

(Bojuwoye et al., 2018). Patients with chronic colitis with inflammatory bowel disease (IBD) are also associated with increased risk of cancer (Keller et al., 2019). In addition to a range of lifestyle factors such as smoking, alcohol intake and increased body weight are also responsible for occurrence of colorectal cancer (Cho et al., 2015). The pharmacological activity of polyphenols against colorectal cancer is tabulated in table 4.

### Gastric cancer

Gastric cancer is the most common cancer throughout the globe especially among older males with an estimated 783000 deaths in 2018 (Rawla and Barsouk, 2019). Gastric cancer has a wide geographical variation and is more prevalent in eastern part of Asia with a global data of 952000 cases per year (Ganguly et al., 2018). Excessive salt intake and consumption of high spicy food is considered to be an important cause of onset of gastric cancer (Shin et al., 2016; Chen et al., 2017). It is also reported that infection of *Helicobacter pylori* results in occurrence of gastric cancer through a number of stages involving atrophic gastritis,

metaplasia and dysplasia (Ishaq and Nunn, 2015). Polymorphisms in genes encoding ethanol and acetaldehyde metabolizing enzymes especially alcohol dehydrogenase (ADH), acetaldehyde dehydrogenase (ALDH) and phase I metabolism-related cytochrome P450 enzyme (CYP450) system are reported to be a cause of gastric cancers (Na and Lee, 2017; Lu et al., 2015). The pharmacological activity of polyphenols against gastric cancer is tabulated in table 5.

### Liver cancers

Hepatocellular carcinoma (HCC) is considered to be the most common primary cancer of liver and is the 6th commonly diagnosed cancer and 4th leading cause of death in the year 2018 with 80% of the cases occurring in sub-Saharan Africa and east Asia (Rawla et al., 2018). Clinical practice reports states that hepatocellular carcinoma accounts to 692000 cases per year which corresponds to 7% of all cancer deaths throughout the world (Aggarwal, 2018). The most important risk factors of hepatocellular

**Table 4.** Pharmacological activity of polyphenols against colorectal cancer

Polyphenols	Experimental system	Important findings	References
Quercetin	Cells: HT-29 colon cancer cell lines.	Cell cycle arrest and induction of apoptosis through up regulation of cleaved caspase 3, Bax, p53 downregulation of Bcl-2 and inhibition of Akt -CSN6-Myc signalling axis.	Yang et al., 2016
caffeic acid phenethyl ester (CAPE)	Cells: RKO, HCT -116, HT-29 and DLD-1 Colon cancer cells.	Inhibition of colon cancer cells by arrest of cancer cells at G1 phase along with retardation of cell invasion along with induction of apoptosis.	Budisan et al., 2019
Apigenin and 5 - Fluoro uracil	Cells: HCT-15 and HT -29 colon carcinoma cells. Animal: Athymic nude mice.	Induction of apoptosis and cell cycle arrest by up regulation of AMP protein kinase (AMPK) along with downregulation of phosphorylated mammalian target of rapamycin (pmTOR), Hypoxia inducible factor -1 $\alpha$ (HIF-1 $\alpha$ ) and Cyclooxygenase.	Sen et al., 2019

**Table 5.** Pharmacological activity of polyphenols against gastric cancer

Polyphenols	Experimental system	Important findings	References
Luteolin	Cells: MKN45 and BGC823 human GC cell.	Induction of cell growth, proliferation, apoptosis by inhibition of Cyclin D1, Cyclin E, Bcl2, MMP2, MMP9, N -cadherin, Vimentin and up regulation of p21, Bax, E -cadherin. Reduction in expression of Notch1, p -PI3K, p-AKT, p-mTOR, p-ERK, phosphorylated - signal transducer and activator of transcription (p -STAT3) and increased expression of tumour suppressor miR -139, miR -34a, miR -422a, miR -107.	Pu et al., 2018
Resveratrol	Cells: SGC7901 and BGC823 gastric cancer cell.	Arrest of migration and invasion in human gastric cancer cells via suppressing metastasis associated lung adenocarcinoma transcript 1 (MALAT1) -mediated epithelial -to-mesenchymal transition.	Yang et al., 2019
Kaempferol	Cells: SNU-216 Human gastric cancer cell.	Suppression of proliferation and promotion of autophagy by up -regulating autophagy related 7 (ATG7), Light chain 3 -II/I (LC3-II/I), beclin 1(BECN1) proteins, miR -181a and inactivation of Mitogen activated protein kinase (MAPK)/ERK and PI3K.	Zhang and Ma, 2019

carcinoma are chronic infections with hepatitis B virus (HBV) or hepatitis C virus (HCV), obesity, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) (Sayiner et al., 2019). The pharmacological activity of polyphenols against liver cancer is tabulated in table 6.

### Esophagus cancer

Esophagus cancer is the 6th leading cause of cancer related death with an estimate of 440000 deaths in the year 2013 (Wang et al., 2018). It is the 8th most common cancer worldwide, largely fatal and overall five year survival ranging from 15% to 20% (Abbas and Krasna, 2017). The highest incidence of esophageal cancer stretches from eastern to Central Asia and vast regions of Indian Ocean coast of Africa and substantial part of South America (Abnet et al., 2018). Smoking, consumption of alcohol, tea and coffee are important risk factors for occurrence of oesophageal cancer (Patel and Benipal, 2018). In addition to it, some bacteria such as *Escherichia coli*, *Fusobacterium nucleatum* is associated with various forms of esophageal cancers (Ajayi et al., 2018). The pharmacological activity of polyphenols against esophagus cancer is tabulated in table 7.

### Cervical cancer

Cervical cancer is the fourth most common among women and the second leading cause of death in women aged between 15-44. It is the first malignant neoplasm recognised by world health organisation which occurs exclusively by viral infection (Cappelli et al., 2018). Recent global studies estimates 527624 new cases with 265672 deaths due to cervical cancer annually with highest rate of incidence in eastern Africa (Zimbabwe) and lowest in western Asia (Shrestha et al., 2018). Human papilloma virus (HPV) is responsible for the occurrence of cervical cancer (Schiffman and Wentzensen, 2013). Other risk factors of cervical cancer include immunosuppressive infections, long-term oral contraceptives and multiple pregnancies (Mofolo et al., 2018). The pharmacological activity of polyphenols against cervical cancer is tabulated in table 8.

### Thyroid cancer

Thyroid cancer is one of the most common malignant endocrine tumours whose incidence has increased

**Table 6.** Pharmacological activity of polyphenols against liver cancer

Polyphenols	Experimental system	Important findings	References
Kaempferol	<b>Cells:</b> HepG2 liver cancer cell.	Inhibition of proliferation, migration, and invasion by decreased expression of MMP -2, MMP-9 and vimentin. Down -regulation of miR -21 and up -regulation of phosphatase and tensin homologue ( PTEN), as well as inactivation of PI3K/AKT/mTOR signalling pathway.	Zhu et al., 2018
Quercetin	<b>Cells:</b> HepG2 liver cancer cell. <b>Animal:</b> BALB/c/nu female mice	Inhibition of Cell proliferation and reduction in tumour volume through regulation of cyclin D1 expression.	Zhou et al., 2019
Apigenin and Hesperidin	<b>Cells:</b> HepG2, HB -8065 liver cancer cells.	Cytotoxicity and damage of DNA increase in oxidative stress accompanied by decrease in expression of Hexokinase 2 and LDHA.	Korga et al., 2019.

**Table 7.** Pharmacological activity of polyphenols against esophageal cancer.

Polyphenols	Experimental system	Important findings	References
Epigallocatechin gallate	<b>Cells:</b> Eca109 and Ec9706 esophageal cancer cells.	Induction of apoptosis by modulating mitochondrial membrane potential and up regulation of caspase -3 activity accompanied by decrease in telomerase activity.	Liu et al., 2017
Luteolin	<b>Cells:</b> EC1, EC9706, KYSE30 and KYSE450 human Esophageal squamous carcinoma cells. <b>Animals:</b> Mice	Decrease in tumour size, arrest of cell cycle through increased expression of p21, p53, bim, Cytochrome C (CYT -C) and cleaved Poly (ADP -ribose) Polymerase (cPARP).	Chen et al., 2017.
Quercetin -3-methyl ether	<b>Cells:</b> SHEE cells, KYSE450 and KYSE510 human esophageal cancer cell. <b>Animal:</b> Fisher 344 rats, human esophageal cancer tissues.	Reduction of inflammation by inhibition of NF - $\kappa$ B and Cyclooxygenase -2 (COX-2) expression. Reduction in hyperplasia through lowering of protein levels of Ki67, c -Jun, p-p70S6K. Inhibition of phosphorylation of mTOR.	Zhao et al., 2018.

**Table 8.** Pharmacological activity of polyphenols against cervical cancer

Polyphenols	Experimental system	Important findings	References
Kaempferol	<b>Cells:</b> HeLa -human cervical cancer cell and HFF (Human foreskin fibroblasts).	Induction of cellular apoptosis through increase in expression of p21, p53, PTEN, Bax and decrease in expression of PI3K, Akt Bcl -2.	Kashafi et al., 2017
Luteoloside	<b>Cells:</b> HeLa human cervical cancer cell, Human normal cells HUVEC12 (human umbilical vein endothelial cell) and LO2 (hepatocyte).	Induction of apoptosis through up regulation of P53, Bax, Caspase and mTOR pathway.	-3 Shao et al., 2018.
Epigallocatechin gallate	<b>Cells:</b> (HPV16/18+), SiHa (HPV16+), CaSki (HPV16+) and C33A (HPV -), HeLa human cervical cancer cells.	Suppression of cervical carcinoma by downregulation of miR -203 and miR -125b and up regulation of miR -210 and miR -29.	Zhu et al., 2019.

**Table 9.** Pharmacological activity of polyphenols against thyroid cancer.

Polyphenols	Experimental system	Important findings	References
Quercetin	<b>Cells:</b> BCPAP papillary thyroid carcinoma cell.	Inhibition of cancer cell through apoptosis, increased levels of cleaved caspase -3, PARP and reduction in levels of Hsp90. Arrest of cell cycle in Sub G1 and S phase.	Mutlu et al., 2016
Genistein	<b>Cells:</b> Nthy-ori 3-1-Normal human follicular epithelial cells, human PTC - derived BHP10 -3 cells (with RET/PTC 1 rearrangement), Human PTC cell lines BCPAP and IHH4 (with BRAF <sup>V600E</sup> mutation)	<b>Conclusion:</b> Induction of cycle arrest through decreased expression of cyclin A2 and cyclin B1. Suppression of epithelial mesenchymal transition and up regulation $\beta$ - catenin in cytoplasm.	Zhang et al., 2019.
Epigallocatechin gallate	<b>Cells:</b> TT, TPC-1 Human thyroid carcinoma cell. <b>Animal:</b> BALB/C nude mice	Inhibition of cell proliferation and induction of apoptosis through increase in Bax/Bcl -2 ratio cleaved caspase -3 and cleaved PARP. Decrease in protein levels of phosphorylated epidermal growth factor receptor (p -EGFR), RAS, p-RAF, p-MEK1/2, and p -ERK1/2.	Wu et al., 2019.

dramatically in past few decades throughout the globe (Liu et al., 2017). There has been a threefold increase in incidence of thyroid cancer from 4.9 to 14.3 per 100000 individuals between the time span of 1975 and 2009 (Olson et al., 2019). There have been projections that thyroid cancer is likely to become third most common cancer in women by 2019 and fourth leading cancer diagnosis by 2030 with two to four times more frequent occurrence in females than in males (Nettore et al., 2018). Exposure to ionizing radiation is an important risk factor for thyroid cancer (Sadeghi et al., 2018). In addition to it, several environmental endocrine disrupting chemicals such as organochlorine pesticides, Phthalates, Bisphenol A, Polychlorinated biphenyls, perfluorinated compounds and heavy metals are presumed to be causal agent thyroid cancer (Fiore et al., 2019). The pharmacological activity of polyphenols against thyroid cancer is tabulated in table 9.

### Bladder cancer

Bladder cancer is the 9th most common cancer in both sexes combined and accounts for 3.1% of all cancer cases in the world (Temraz et al., 2019). In 2016, global estimates reported 437442 incidences and 186199 deaths related to bladder cancer with annual standardized incidence rate of 6.69 per 100000. Globally, the increase rate is 64% between the time span of 1990 and 2016 (Ebrahimi et al., 2016). Most bladder cancer arise secondary to exogenous exposure to carcinogens through the respiratory system, gastrointestinal tract and skin contact. The most common risk factors of bladder cancer are tobacco smoke and occupational and environmental carcinogens (Cumberbatch and Noon, 2019). In addition to smoking people working in rubber and dye industry are also susceptible to bladder cancer due to constant exposure of

harmful chemicals like ortho-Toluidine, aniline, 2,4-xylidine, para-toluidine, ortho-anisidine or ortho-chloroaniline (Nakano et al., 2018). The pharmacological activity of polyphenols against bladder cancer is tabulated in table 10.

### Non Hodgkin lymphoma

Non Hodgkin lymphoma ranks 10th and 12th most frequent cancer in the world amongst male and female respectively with an estimated 509,590 new cases and 248,724 deaths in 2018 (Miranda-Filho et al., 2019). It is the most common hematologic malignancy in the world and is more common in developed country having more than 40 major subtypes with distinct genetic, morphologic, and clinical features (Chihara et al., 2015). Congenital and acquired states of immunosuppression are strongest factors that may result in non-Hodgkin lymphoma (Chiu and Hou, 2015). In addition to it, Epstein Barr virus is also considered to be one of the risk factors of non-Hodgkin lymphoma (Teras et al., 2015). The pharmacological activity of polyphenols against Non Hodgkin lymphoma is tabulated in table 11.

### Pancreatic cancer

Pancreatic cancer is an intractable malignancy and is the 11th most common cancer in the world counting 458,918 new cases and causing 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 (Rawla et al., 2019). It is one of the most fatal type cancers in the world with a five-year relative survival rate of 8% (Saad et al., 2018). Hereditary unmodifiable factors are major risks of pancreatic cancer. They include (a) HBOC (Hereditary breast and ovarian cancer syndrome) with mutations in BRCA1 and BRCA2 and accounts for 17-19% of pancreatic cancers (b) HNPCC (Hereditary Non Polyposis Colorectal Cancer or Lynch syndrome) having microsatellite instability (MSH2, MSH6, MLH1, PMS2 and EPCAM genes), (c) FAP (Familial Adenomatous polyposis), caused by a mutation in the Adenomatous polyposis coli (APC) gene, (d) PJS (Peutz-Jeghers Syndrome) with mutations in Serine/threonine kinase 11 (STK11) / Liver Kinase B1 (LKB1) gene and characterized by hamartomatous polyposis syndrome, (e)

**Table 10.** Pharmacological activity of polyphenols against bladder cancer

Polyphenols	Experimental system	Important findings	References
Quercetin	<b>Cells:</b> Bladder cancer cell lines	Induction of apoptosis and anticancer activity through modulation of AMPK pathway.	Su et al., 2016
Kaempferol	<b>Cells:</b> EJ bladder cancer cell line	Arrest of cell cycle through downregulation of S <sub>2</sub> -phase related proteins (Cyclin D1 and CDK6) and up regulation of p21, p27, p53 and p38. Induction of apoptosis by up regulation of pro-apoptotic proteins (Bax and Bad) and downregulation of anti-apoptotic proteins (Bid, Mcl-2, and Bcl-xL). Decrease in levels of p-AKT.	Wu et al., 2018.
Epigallocatechin gallate	<b>Cells:</b> T24 and 5637 human bladder cancer cells, <b>Animal:</b> BALB/c nude mice	Inhibition of proliferation and induction of apoptosis by downregulation of PI3K/Akt and up regulation of PTEN accompanied by decrease in tumour weight.	Luo et al., 2018.

**Table 11.** Pharmacological activity of polyphenols against non-Hodgkin lymphoma

Polyphenols	Experimental system	Important findings	References
Epigallocatechin gallate	Cells: MCL Jeko-1 and BL Raji cell lines	Inhibition of cell growth and induction of apoptosis through increase in caspases activity accompanied by downregulation of Bcl-2 and up regulation of Bax both at mRNA and protein levels.	Wang et al., 2015.
Resveratrol	<b>Cells:</b> Extranodal NK/T cell lymphoma (NKTCL) cell lines SNT-8, SNK-10, and SNT-16 cells.	Induction of cell cycle arrest through inhibition of cyclin A. Induction of apoptosis through downregulation of Mcl-1 and survivin while up regulation of Bax and Bad. Modulation of Akt pathway.	Sui et al., 2017.

**Table 12.** Pharmacological activity of polyphenols against pancreatic

Polyphenols	Experimental system	Important findings	References
Quercetin-3-O-glucoside	Cells: CFPAC-1, pancreatic ductal adenocarcinoma cells	Anticancer activity through Inhibition of Transforming growth factor $\beta$ 1 (TGF- $\beta$ 1) or Vascular endothelial growth factor-A (VEGF-A) induced migration of cancer cells. Decreased phosphorylation levels of focal adhesion kinase (FAK) and ERK1/2.	Lee et al., 2016
Naringenin	Cells: Human pancreatic cancer SNU - 213 cell lines.	Induction of apoptosis through modulation of caspases, up regulation of proapoptotic Bak and down regulation of pro survival Bcl-xL. Increase in levels of apoptotic protein marker CytC, apoptotic protease activating factor -1 (Apaf-1) along with Up regulation of JNK, p38 and p53 proteins.	Park et al., 2017
Isorhamnetin	Cells: PANC-1 Pancreatic cancer cell lines.	Induction of cell cycle arrest and down regulation of cyclins, cdks and inhibition of phosphorylation of MEK.	Wang et al., 2018

AMMM (Familial Atypical Multiple Mole Melanoma syndrome), characterized by malignant melanoma in one or more first-degree or second-degree relatives, (f) HP (Hereditary Pancreatitis), characterized by mutations in PRSS1 gene, (g) CF (Cystic Fibrosis) with mutations in Cystic fibrosis transmembrane conductance regulator (CFTR) gene (Capasso et al., 2018). Table 1 illustrates the pharmacological activity of selected polyphenols against the cancers discussed in this article. The pharmacological activity of polyphenols against pancreatic cancer is tabulated in table 12.

### Mechanism of action of polyphenols against cancer

Reactive oxygen species are spontaneously generated in all biological system in response to a wide array of biochemical processes and play an important role in intracellular cell signalling and homeostasis. The human body is equipped with an elaborate antioxidant system that maintains proper balance of reactive oxygen species thereby conferring protection to the cells. Cancer is one of the important diseases that are caused fundamentally due to oxidative stress and imbalance of antioxidant machinery (Pizzino et al., 2017). The processes through which polyphenols exert their anticancer activity are vast. It does so by interacting and inhibiting wide range of biomolecules and biochemical pathways. In this review, efforts have been taken to illustrate the inhibitory and suppressive action of polyphenols on some of the important biochemical pathways and molecules related to progression of cancer.

### Inhibition of Inflammatory processes

#### *Inhibition of Nuclear Factor- $\kappa$ B (NF- $\kappa$ B)*

The characteristic feature of most cancer is uncontrolled cell proliferation followed by metastasis which is controlled by a number of biochemical pathways. Thus the strategy of controlling cancer lays in inhibition of one or more biochemical pathways by polyphenols. A link between inflammation and establishment of tumour is well established (Ritter and Greten, 2019). NF- $\kappa$ B is a ubiquitous transcription factor found in all animal cell types and plays an important role in inflammation processes. In unstimulated cells NF- $\kappa$ B is located in the cytoplasm as an inactive heterodimer composed of two subunits namely p50 and p65 which in turn forms a complex with inhibitor of kappa B (I $\kappa$ B- $\alpha$ ) or I $\kappa$ B- $\beta$ , retaining it in the cytoplasm (Karunaweera et al., 2015). A wide range of stimuli can activate NF- $\kappa$ B pathway and depending upon the nature of stimuli, the activation of NF- $\kappa$ B signalling pathway may be classified into canonical, non-canonical and atypical modes. All the processes lead to activation of NF- $\kappa$ B dimers and its translocation into the nucleus to activate target gene transcription which results in production of proinflammatory compounds and ultimately inflammatory responses. It has been observed that polyphenols play a crucial role modulation of NF- $\kappa$ B pathway by inhibiting I $\kappa$ B kinase (IKK) activation, nuclear translocation of activated NF- $\kappa$ B, proteosomal degradation of I $\kappa$ B, and binding of NF- $\kappa$ B to DNA (Yahfoufi et al., 2018). This results in inhibition of production of proinflammatory metabolites responsible for inflammatory responses.

### **Inhibition of Cyclooxygenase (COX) and Lipoxygenase (LOX)**

Acute inflammation also has a very intimate relation with arachidonic acid pathway. In humans, arachidonic acid are mainly released from membrane phospholipids by phospholipase A2 phospholipase C and phospholipase D (Hanna and Hafiz, 2018) and acts as a substrate of LOX to generate hydroperoxyeicostatetraenoic acids, leukotrienes, and Lipoxins or COX to produce prostaglandin G2 and prostaglandin H2 which is further converted into other forms of prostaglandins (Borin et al., 2017). Recent studies report that COX-2 contributes to the metastatic properties of gastrointestinal malignancies (Nagaraju and El-Rayes, 2019). Apart from this cyclooxygenase also act upon arachidonic acid to generate thromboxane A2 which is associated in cancer-associated inflammation, tumour progression, and metastasis (Dovizio et al., 2014; Orr et al., 2016). Prostanoids are mostly associated with occurrence of cancers (Madrigal-Martínez et al., 2019). Promotion of invasion and metastasis of gastric cancer cell and tumourigenesis in mammary gland are brought about by 12-Lipoxygenase (Zhong et al., 2018). The metabolites of 5-lipoxygenase also have a prominent proinflammatory role in a number of pathological conditions including atherosclerosis, Alzheimer's disease, type 2 diabetes and cancer (Moore and Pidgeon, 2017). A recent study reported the inhibitory activity of dietary polyphenols on COX-2 expression, levels of IL-1 $\beta$ , IL-6, IL-8 and TNF- $\alpha$  in colorectal cancer (Owczarek and Lewandowska, 2017). Molecular docking analysis revealed that polyphenols inhibit the activity of COX-2 by binding with S530, R120 and Y385 residue of their amino acid chain (Dash et al., 2015). Similarly structure functional relationship of polyphenols reveals that presence of ortho hydroxyl group in their A ring and B ring and presence of 2, 3 double bonds are responsible for inhibition of Lipoxygenase activity (Ribeiro et al., 2014).

### **Inhibition of Phosphoinositide 3-Kinase (PI3K)/Akt pathway**

Akt is a serine/threonine kinase consisting of three isoforms namely Akt1, Akt2, and Akt3. PI3K/Akt pathway is one of the most intensively investigated pathways in relation to its cancer due to its potential role in cell growth, cell cycle progression, survival and apoptosis (Chen et al., 2018). Anomalies in expression and function of Akt are related to a number of cancers. Studies indicate that amplification of Akt1 gene occurs in gastric carcinoma (Matsuoka and Yashiro, 2014), adenocarcinoma and glioblastomas (Wang et al., 2016) and prostate cancer (Silva-Oliveira et al., 2017), whereas Akt2 amplification is reported in head and neck squamous cell carcinoma (García-Carracedo et al., 2016), colorectal, pancreatic, ovarian and breast cancers (Banno et al., 2017). Akt3 expression is up regulated in androgen resistant prostate cancer cells, estrogen receptor deficient breast cancer cells and

metastatic melanoma cells (Rodgers et al., 2017). Impairment in autophagy is one of the causes of cancer progression. Studies report that Akt activated Mammalian target of rapamycin (mTOR) signalling pathway negatively regulates autophagy and blockage of PI3K/Akt/mTOR signal results in induction of autophagy signals and reduction in angiogenesis (Yu et al., 2017). Numerous studies indicate the modulation of PI3K/Akt pathway by polyphenols. Studies indicate that polyphenols exert their anticancer inhibitory activity largely by down regulating PI3K/Akt and inducing suitable atmosphere for initiation of autophagy. A study reported that apigenin inhibited the expression of Akt, PI3K, and NF- $\kappa$ B p105/p50 proteins and phosphorylation of pAkt (Erdogan et al., 2016). Decrease in phosphorylated Akt and mTOR in hepatocellular carcinoma cells have also been reported upon treatment with apigenin ultimately resulting in induction of autophagy (Yang and Wang, 2018). From mechanistic point of view, polyphenols inhibit PI3K by competing with adenosine triphosphate (ATP), i.e. they act as competitive inhibitors. Most of the inhibitors bind to the active site of PI3K thereby rendering it unavailable for ATP. The PI3K contains three region in its active site namely the hinge region (Val882), the affinity pocket (Lys833, Asp841, Tyr867, Ala885, Ser806, Tyr867) or the back pocket (DFG-motif, gate keeper and catalytic lysine) and the ribose pocket (Met804, Ala805, Lys802, Met953, Asp964, Trp812, etc.) and accordingly the inhibitors interact with any of these regions (Liu et al., 2017). Quercetin is reported to bind with the ATP binding site PI3K to exert its inhibitory action (Russo et al., 2017). A recent study indicated that flavonoids regulate the activity of Akt by inhibiting Pleckstrin homology (PH) domain and PIP3 interaction. In silico analysis revealed that flavonoids forms hydrogen bonds at various positions in the Akt-PH domain to bring about the inhibition process (Kang et al., 2018). Another study also states that flavonoids also bind with PH domain of 3-phosphoinositide-dependent kinase (PDK1) and cause inhibition of activity. It was observed that hydroxyl group at 3' and 4' position of flavonoids mostly interacts with Lys465 and Arg521 of the PDK1-PH domain through hydrogen bonds and thus inhibits the interaction of PIP3 (Kang et al., 2017).

### **Inhibition of Mammalian target of rapamycin (mTOR)**

Mammalian target of rapamycin (mTOR) is an evolutionary conserved serine/threonine kinase and acts as an important regulator of cell growth and proliferation (Plaquette et al., 2018). Studies indicate that polyphenols acts as an inhibitor of mTOR. It has been reported that resveratrol induces autophagy and inhibits mTOR by

competing with ATP (Park et al., 2016). The inhibition of mTOR by resveratrol is brought about by promoting the association between mTOR and its inhibitor DEPTOR thereby rendering the complex inactive (Liu et al., 2010). Epigallocatechin gallate was also reported to be an ATP competitive inhibitor of mTOR (Holczer et al., 2018).

#### **Inhibition of B-Cell Lymphoma (Bcl) family of protein**

The anticancer activity of polyphenols is also frequently brought about by inhibition of BCL-2 family of protein. BCL-2, Bcl-xL, MCL-1 blocks apoptosis while Bad, Bax, Bid, Bim are responsible for promotion of apoptosis (Campbell and Tait, 2018). A recent report states that polyphenols have an inhibitory action towards antiapoptotic BCL-2. Molecular docking analysis revealed that polyphenols bind to the hydrophobic groove of BCL-2 to exert its inhibitory affect (Verma et al., 2017).

#### **Inhibition of regulatory molecules of cell cycle**

Another mechanism by which polyphenols express their anticancer mechanism is by stopping at various stages of cell cycle so that damaged DNA are not replicated into the progeny cells. In mammals, the cell cycle is highly regulated and involves a series of protein complexes (cyclins and CDKs) and check points. Cyclin and Cyclin dependent Kinase (CDKs) forms complexes and drives the progression of cell cycle through four phases namely mitosis, G0G1 phase, DNA synthetic phase (S-Phase) and G2 phase (Zheng, 2019). Majority of mammalian cells don't enter the cell cycle and progression but in case of malignancies, the control over progression of cell cycle is lost resulting in uncontrolled proliferation and unrestricted cell phase transition ultimately leading to altered behavior. Polyphenols are reported to inhibit the cell cycle progression by reducing the levels of one or more cell cycle proteins or arresting the progression of cell cycle. A recent study indicates that flavonoids acts as an inhibitor of CDK6 by competing with ATP and binding with ATP binding site resulting in stoppage of activity of CDK6/CyclinD complexes. Strong hydrogen bonds are formed between CDK6 and B-ring 3', 4' hydroxyl groups of the flavonoids rendering them inactive for further activity (Zhang et al., 2018). Molecular docking also revealed that flavonoids have a potential to bind with CDK1 with the B ring turned towards the C-helix and its 4' hydroxyl group bonded to the Glu51, Lys33 and or Asp146 of the side chain of C helix which enable the flavonoids to act as competitive inhibitors of CDK1 Navarro-Retamal and Caballero, 2016). Flavopiridol, a representative of flavonoids also binds to CDK2 and acts as a competitive inhibitor (Li et al., 2015).

#### **Inhibition of Epithelial Mesenchymal Transition (EMT)**

Another strategy of cancer prevention by polyphenols in inhibiting the EMT. It is a process in which multiple biochemical changes in a polarized epithelial cells results in acquiring of mesenchymal cell characteristics with enhanced migratory

capacity, invasiveness, elevated resistance to apoptosis and increase in production of extracellular matrix (ECM) components. The process culminates in total degradation of underlying basement membrane and the formation of a mesenchymal cell which can migrate anywhere from the source epithelial layer (Kalluri and Weinberg, 2009). E-cadherins are important components of adherens junction and play an important role in cell adhesion and maintaining epithelial phenotype of cells (Mendonça and Na, 2018) E-cadherin is a well-known tumour suppressor protein and loss of its expression accompanied by EMT occurs frequently during tumour progression and metastasis (Petrova et al., 2018). N-cadherin also a representative of classical adherins and is typically absent or expressed in very low levels in normal epithelial cells, its increased expression leads to a number of cancer and tumour aggressiveness (Mrozik et al., 2018). It is reported that N-cadherin plays an important role in epithelial mesenchymal transition (Wang et al., 2016). Polyphenols have been reported to up regulate the expression of E-cadherin and suppress N-cadherin thus preventing metastasis.

#### **Inhibition of Matrix metalloproteinases (MMPs)**

Inhibition of matrix metalloproteinases is another way by which cancers can be inhibited. Matrix metalloproteinases (MMPs) are main enzymes that are responsible for degradation of collagen and other materials of extracellular matrix (Jabłońska-Trypuć et al., 2016). Polyphenols play a major role in inhibition of these matrix metalloproteinases. Molecular docking analysis of resveratrol with MMP-2 and MMP-9 revealed that resveratrol occupied the active sites of MMP-2 and MMP-9. It was further observed that Leu 164, Ala 165 and Thr 227 were engaged in case of MMP-2 while Glu 402, Ala 417 and Arg 424 were engaged in H-Bonding with resveratrol in case of MMP-9. Reports also states that galloyl group of EGCG have high binding affinity with pro-active MMP-9 and thus accounts for inhibitory activity (Sarkar et al., 2016).

#### **Inhibition of Vascular Endothelial growth factor (VEGF)**

Vascular endothelial growth factor and its receptor (VEGF-VEGFR) system play an important role in regulation of angiogenesis and lymphangiogenesis in vertebrates. It is reported that VEGF is over expressed in many solid cancers and inhibition of VEGF can inhibit cancer in many model system (Zirlik and Duyster, 2018). A recent in-silico study reported that epigallocatechin-gallate binds to a groove at the pole of VEGF and interacts with interact with 13 residues on both subunits of VEGF and form hydrogen bonds with three residues (Asp34, Lys48 and Ser50) to exert its inhibitor action (Moyle et al., 2015). The potency of inhibition by

polyphenols is strongly related to presence of a galloyl group at 3 position of flavan-3-ols; the degree of polymerisation of procyanidin oligomers; the presence of a C2=C3 double bond in the C-ring, especially if conjugated with the 4-oxo group (flavones and flavonols); the total number of hydroxyl groups on the B-ring; the presence of the catechol group on the B-ring; hydroxylation of position 3 on C-ring; lack of further substitution of hydroxyl groups on the B-ring (Cerezo et al., 2015).

### Conclusion

Cancer is a matter of great concern in present day world and its complicity is ever increasing day by day and the diversification of remedial strategies are also gearing up side by side. Since plant is a source of wide array of natural products having anticancer activity, efforts are being made to pool anticancer drugs from the plants. The review highlights the anticancer activity of a number of polyphenolic compounds from plant origin used as an anticancer agent. Though satisfactory results have been obtained through In-vitro studies and some in vivo studies using laboratory animals as model system, however human trials are largely lacking. Thus efforts are required to test the activity of these compounds on humans using standard operating and ethical measures. In addition to it, further investigation on the inhibitory mechanisms of polyphenols on the biochemical pathways associated to cancers are required using state of art molecular and in-silico tools. It is to be noted that some cancer also possess harmful effect and therefore use of these polyphenols for treatment of cancers should be dealt with caution. In addition to overhauling the research approaches, changes in food habit and life style patters of humans also requires special emphasis in order to make a holistic approach in combating cancer using polyphenols as an important tool.

### Conflict of interest

The author declares no conflict of interest.

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