Role Of Flavonoids In Cancer Prevention: Chemistry And Mode Of Action

Harpreet Kaur[*1], Tanu Bansal[1],

[1]*Department of Chemistry, Lovely Professional University, Phagwara-144411, Punjab India*
Corresponding author Email: harpreet2.kaur@lpu.co.in

ABSTRACT: Plants derived compounds have been successfully used as anti-cancer medicine so far. Paclitaxel, pomiferin, roscovitine are the few examples of plant derived drugs. There are a number of plant constituents which are being studied for their anticancer activity and still there are a number of natural products that are under various stages of clinical trial. Many researchers are working on these compounds so as to find out their mode of action and selectivity of cancer cell line. Exhaustive work is being done to get promising anti-cancer agents in future. In the present review, naturally occurring flavonoids have been considered and their role in controlling cancer is being investigated. A study of their mode of actions and categorization of their molecular targets have been done.

Keywords: paclitaxel; pomiferin; roscovitine; cancer cell lines; flavonoids; anti-cancer.

INTRODUCTION

Cancer is an uncontrolled growth of abnormal cells anywhere in the body. And today with modernisation and changing environment, the rate of cancer in the human body is increasing at a very fast pace. Presently, 250 drugs are available in the market for the treatment of cancer and their related problems. With the rate of increase in the cancer patients, researchers have become more and more active in the area of forming and finding new therapies or drugs to work against cancer. Various treatments are known to cure the disease like surgery, chemotherapy. But new ways are required to deal with the problem and hence a lot of work is in progress to find out the solution. Thousands of compounds are being screened to find out their efficacy against various kinds of cancer. Still, there is requirement of new compounds that can combat this serious problem.

Plants have been known to yield new compounds with potency to fight against cancer. From the era of Unanis and Ayurveda various diseases were cured with constituents of plants and tribal people relied on plants for treatment of their several diseases. Plants based products have emerged as effective anti-cancer agents as well. Almost 60% of the prevailing drugs for the treatment of cancer are derived from natural resources like marine organisms, fungi, plants *etc*.(Cragg & Newman, 2005, Raza *et.al.*, 2015). There are large numbers of such natural agents which are under the preclinical stage of development. The compounds mainly derived from the secondary metabolites of plants like alkaloids, flavonoids, polyphenols, lignans etc. Since large compounds are part of flavonoid family which are very effective and under the preclinical trials, the review is focussing the various flavonoid constituents derived from plants which shows anti-cancer properties. Flavonoids are the polyphenolics with low molecular weight found in various parts of the plants. They are abundantly present in many foods and beverages like onion, tea, etc. hence are also known as dietary flavonoids. They are responsible for coloration in plants and protect them from insects. Also, in plants, flavonoids inhibit various stresses like biotic or non-biotic. The structure of flavonoids includes C_6-C_3-C_6 framework. It includes the benzene ring attached to benzopyran moiety and depending on its position, its degree of oxidation and heterocyclic ring saturation they are classified into

various classes as shown in figure1 like flavane, dihydroflavanol, flavanone, flavone, flavanol, isoflavanoids , neoflavanoids *etc*.(Samanta & Das, 2011). Flavanoids play wider role in plants. They act as detoxifying agents, signal molecule, stimulants for spore germination, allelochemical agents, pollinator attractants, UV filters and many more as shown in fig 2 (Samanta & Das, 2011). They are taken by humans from long time and due to its low water solubility, they are intoxicated in the body and are responsible for curing many diseases. It shows various biological activities like antioxidants, hepatoprotective, anti-bacterial, anti-inflammatory, anti-viral as well as anti-cancer (Shashank & Pandey, 2013).
In the present review various flavonoids showing anti cancer activity are compiled depending on their type of flavanoid, their cure for type of cancer and their mode of action.

Flavonols

Flavonols have the skeleton structure of 3-hydroxyflavone. They are the class of flavonoids that has cancer preventive effects (Multiethnic & Study, 2007) (Fig 3). They act as antioxidants as well as prevent auto-oxidation of ascorbic acid but leads to decolouration (Herrmann, 1976).

Flavones

It is the class of flavonoids with the backbone structure of 2-phenylchromen-4-one as shown in Fig 4. It is mainly present in red or purple food and spices. They have no antioxidant food value and neither have any physiological effect(Lotito & Frei, 2006). They shows the effect on enzymes CYP(P_{450}) which are responsible for metabolism of drugs(Si et al., 2009).

Flavanols:

The skeleton of flavanol is 2-phenyl-3,4-dihydro-2*H*-chromen-3-ol, they are derivatives of flavanes. In diet they are provide by fruits, vegetables and wine(Ruidavets, Teissedre, & Ferrie, 2000). Few anticancer flavanols have been depicted in fig 5

Flavanone

They are derived from flavones. Citrus flavanones show many biological activities like anti-oxidant, anti-inflamatory, cardiovascular properties, anti-microbial etc.(Barreca et al.). Figure 6 shows few representive of this class having anticancer activity

Isoflavones

Isoflavones are naturally occurring isoflavanoids(Kaufman, Duke, Brielmann, Boik, & Hoyt, 1997) and sold as dietery supplements. They also act as phytoestrogens in mammals(Thompson et al., 2009). Ginstein (Figure 7) is an active anticancer agent.

Anthocyanidin

They are water soluble plant pigment, responsible foe the colouration of fruits and vegetables, therefore also used as natural colourant. They possess anti-oxidative, anti-microbial activity and also show cure against non-communicable diseases(Khoo, 2017) (Figure 8)

There are different mechanisms by which the anti- cancer agents work, depending upon the presence of different initiators and enzymes present on the surface of the cells. The present review focuses on the detailed study of the molecular mechanisms by which the flavonoids work as anti-cancer.

MODES OF ACTION

Cell cycle arrest

The cell cycle is regulated by a series of steps which helps in cell cycle progression. DNA synthesis is the S-phase and then the separation into daughter cells is M- phase and the time taken in between these two phases is G2 phase. G2 phase is very important phase. During this phase cells can check their error in DNA replication or propagation. While phase G1 is where duplication of DNA occurs from mitogen signals. Any kind of inhibition at G1/S phase or G2/M phase in cancer cell lines led to the induction of cell cycle arrest. Apigenin, baicalin,

baicalein and wogonin show cell enhancement in treatment of G2/M arrest and cause proliferation in pancreatic cancer cell line. And also it shows the G1/G2 arrest in case of rat endothelial cells of heart (Paper, 2009). The figure 9 exhibits flavonoids that inhibit cell growth by arresting cell cycle at different phases.

Inhibition of mutant p53

Tumor protein p53 is a protein that regulates the cell cycle. This is also known as tumor suppressor as it prevents the formation of cancer cell by regulating gene expression in normal cells (Surget & Bourdon, 2014). Mutation or abnormal expression of p53 led to the formation and progression of cancer cells due to a genetic abnormality. Flavonoids help with down regulating the expression of p53 protein, thus allowing the inhibition of cell cycle and thereby apoptosis of cells.

Tyrosine kinase inhibition

The family of protein called tyrosine kinase helps in transferring growth factor signals to the nucleus. They are tumors, genetic causing the abnormal growth of cell which led to tumor. Its inhibition controls the unregulated growth of the cells as shown in figure 10.

Luteolin and quercetin (Levy, Teuerstein, Marbach, Radian, & Sharoni, 1984) both acts as tyrosine inhibitor, which is induced by EGF (epidermal growth factor) responsible for the growth of cancer cell. The dephosphorylation of EGFR led to the inhibition of tumor growth on hepatic, pancreatic, breast and skin cancer cell lines. Such effect is also shown by genistein, taxofolin, d- catechin but lesser than the those of above flavonoids.(Huang, 1999)

Estrogen receptor binding

There are two types of Estrogen Receptors (ER): ER alpha and ER beta found on cell surface, these are being shown to be activated by hormone estrogen. After activation ER translocate inside the nucleus and regulates the gene expression by binding to DNA(Levin, 2015). Estrogen receptor-α boosts the growth of breast cancer cell by targeting the insulin like growth factor system. Therefore, to stop the growth of this cancer cell the inhibition of ER-α is required. For instance, apigenin increases the rate of ATF3 in mRNA and thereby suppressing the factor Id1 in ovarian tumour cell lines and causing their anti-proliferation. Therefore ER consider as a transcriptional regulator in breast cancer.

Heat shock protein inhibition

These protein associate with the cancer cells and stop the process of apoptosis thereby causing the survival of cancer cells. These are generated during the body stress. So binding these proteins with the inhibitor control the de apoptosis process and results in degradation. HSTCP1 and hsp70-1, the anti-apoptotic heat shock proteins showed decrease in level when exposed to quercetin leading to apoptosis in cancer cells(Wenzel, Herzog, Kuntz, & Daniel, 2004).

Inhibition of protein

Ras is one of the oncogene having function of regulating the growth of cells. Any type of mutation in this protein led to uncontrolled growth of cells and led to the tumour. That is why any constituent which inhibits the Ras protein or stop the mutation of it can deregulates the growth in cancer cell lines. Quercetin inhibits the protein expression of p21-Ras. p21-Ras promotes the growth of human colon cancer cells(Wenzel et al., 2004). Apigenin inhibit the GLUT-1 mRNA (glucose transporter 1) and thereby downregulates the Akt protein expression thereby following PI3K/Akt pathway in lung, ovarian, breast and pancreatic cancer. Cell lines of all gliomas also follow inhibition of P13K/Akt pathway for suppressing the cell proliferation by overexpression of MiR-181b which target the IGF-1R (insulin like growth factor 1 receptor basically tyrosine kinase receptor)(Shi et al., 2013).

Angiogenesis

Angiogenesis is the physiological process in which new vessel formation take place from the pre-existing vessels. It is the controlled process in human body. The growth of new blood vessels takes place which need expansion and stabilization of vascular endothelial cells. Various factors control them like angiogenic and angiostatic. The process helps in transition of benign tumour to malignant tumour cell. Therefore it is considered as a key target in cancer treatment. Inhibition of vascularization process cause death of cell, which can balance the rate of cell proliferation. Studies suggested that flavonoids supress angiogenesis by down regulating the expression of VEGF(Don et al., 2013).

Activity inhibition of DNA polymerase or topoisomerase

Topoisomerase is the enzyme that regulates the unwinding of the DNA during replication process. Studies had found that there are some molecules that inhibit the DNA replication by inhibiting the topoisomerase activity. The triterpenes with a carboxyl group inhibit the activities of topoisomerase II, while the triterpenes with a ketone group suppressed the activities of topoisomerase II(Mizushina et al., 2003). cEPA (eicosapentaenoic acid) inhibit the growth of polymerase and topoisomerase which are involved in DNA replication process. They block the starting step of G1 phase and boost cyclin E level of protein. This led to the inhibition of DNA replication and apoptosis (Figure 11).

Downregulation of Bcl-2 and Bcl-X(L) expression

These are two ant apoptotic proteins whose downregulation cause the spontaneous death of cells. Bax triggers the process of apoptosis therefore any flavonoid that increase the Bax and decrease the Bcl-2 and Bcl-X(L) cause the process of apoptosis. In case of prostate cancer cell lines the same process occurs by the flavonoid apigenin (Yan, Qi, Li, Zhan, & Shao, 2017).

There are metabolizing enzymes as well as certain protein present in the cancer cell lines responsible for their growth. By using some selective biochemical inhibitors their work could be controlled and helps in cancer cell death (Figure 12).

Decrease in mitochondrial membrane potential

When mitochondrial membrane disrupts, it releases the cytochrome c which induces the process of apoptosis. Leutolin acts on membrane and cytochrome c is released and activates caspase-3 and caspase-9 causing the downregulation of Bcl-2 and Bcl-x(L) and inducing apoptosis in HL-60 cell(Lin, Shi, Wang, & Shen, 2008). Cirsilineol activates caspase-3 and 9 and causes the cleavage of PARP thereby causing apoptosis via mitochondrial pathway in ovarian, prostate, hepatic and uterus cancer cell lines(Sheng, Sun, Yin, Chen, & Xu, 2008).

Induction of CYP enzyme

Mainly CYPs are considered as promoters of cancer but in some cases, few flavonoids act on it causing the induction of CYP1A1 and CYP1B1 enzymes and thus causes cell death via CYP1 mediated metabolism. For example eupatorin and cirsiliol both inhibit the growth of breast cancer cells (V. P. Androutsopoulos, Li, & Arroo, 2009). Quercetin also inhibit the CYP3A4 and 1A2 activities without showing any effect on 2E1 in Hep G2 cells(Rodgers & Grant, 1998).

Cleavage of PARP

Poly (ADP-ribose) polymerase (PARP) is responsible for the repair of DNA, gene stability and the cell death. The cleavage of PARP inhibits Caspase-3 and caspase-7 repair and lead to cell death. Eupatorin works in similar manner in HeLa cell lines and causes G2/M phase cell cycle arrest (K. Lee, Hyun Lee, Jung, Shin, & Lee, 2016).

Inhibition of tubulin polymerisation

Microtubules present in eukaryotic cells play an important role in mitosis. They work at different stages of cell cycle forming the microtubule dynamics for cell growth. Basically it has two sub units α and β- tubulin. Any inhibitor that inhibits or interrupts this dynamics

results in cell death. Flavonoid acts as tubulin polymerisation inhibitors. Eupatin works on the process and cause apoptosis in NCi-60 cancer cell lines (Beutler et al., 1998).

Increase in p21:

P21 is the cyclin dependent kinase (Cdk) inhibitor which inhibits all the cyclin complexes and thereby causing DNA damage to cell cycle arrest. Apigenin inhibit the G2/M phase cell cycle progression by increasing the interaction between $p21^{WAF1/CIP1}$ and PCNA (proliferating cell nuclear antigen)(Tseng et al., 2017). Casticin helps in increase of p21 expression causing the inhibition of Cdk and results in apoptosis in breast cancer cells(Ferreira, Luthria, Sasaki, & Heyerick, 2010).

Anti-cancer treatment could be evolved by targeting any mode of action mentioned above. Table-1 compiles the mode of action of different type of flavonoids as anti-cancer agent.

CONCLUSION

Plants provide the best option to give variety of compounds. Not only the flavonoids but also other forms likes alkaloids, terpenoids *etc.* have been proven to be effective. Still many of the medicinal plants are to be investigated that have potential to give compounds having cancer preventing ability. From the above review we can conclude that plants provide large number of flavonoids that have anti-cancer activities and these can be used to prevent the disease for the betterment of the mankind. Few of them are under clinical trial so these can be used as drugs. The modes of action of lead molecules have been summarized with the objective of providing a database that can be utilized extensively for new drug development. This review could be used by researcher for synthesis as well as isolations of new lead molecules. The present work would be very helpful and useful for those who intend to develop anticancer drugs.

Conflicts of interest:

There is no conflicts of interest associated with the present work.

References

Androutsopoulos, V., Arroo, R. R. J., Hall, J. F., Surichan, S., and Potter, G. A. (2008). Antiproliferative and cytostatic effects of the natural product eupatorin on MDA-MB-468 human breast cancer cells due to CYP1-mediated metabolism. Breast Cancer Res., *10*(3), 1–12.

Androutsopoulos, V. P., Li, N., and Arroo, R. R. J. (2009). The methoxylated flavones eupatorin and cirsiliol induce CYP1 enzyme expression in MCF7 cells. J. Nat. Prod., *72*(8), 1390–1394.

Arisawa, M., Hayashi, T., Shimizu, M., Morita, N., Bai, H., Kuze, S., and Ito, Y. (1991). Isolation and cytotoxicity of two new flavonoids from chrysosplenium grayanum and related flavonols. J. Nat. Prod., *54*(3), 898–901.

Arisawa, M., & Shimizu, M. (1995). Inhibition of Tumour-promoter-enhanced into Cellular Phospholipids by Flavonols from Genus Chrysosplenium, *9* th February 1994), 222–224.

Bandyopadhyay, S., Romero, J. R., & Chattopadhyay, N. (2008). Kaempferol and quercetin stimulate granulocyte-macrophage colony-stimulating factor secretion in human prostate cancer cells. Mol Cell Endocrinol, 287(1–2), 57–64.

Barreca D., Gattuso G., Bellocco E., Calderaro A., Trombetta D., Smeriglio A., Laganà G., Daglia M., Meneghini S., and Nabavi S.M .(2017). Flavanones : Citrus phytochemical with health-promoting properties, Biofactors. 43(4), 495-506.

Beutler, J. A., Cardellina, J. H., Lin, C. M., Hamel, E., Cragg, G. M., and Boyd, M. R. (1993). Centaureidin, a cytotoxic flavone from Polymnia fruticosa, inhibits tubulin polymerization. Bioorg Med Chem Lett, 3(4), 581–584.

Beutler, J. A., Hamel, E., Vlietinck, A. J., Haemers, A., Rajan, P., Roitman, J. N., and Boyd,

M. R. (1998). Structure-activity requirements for flavone cytotoxicity and binding to tubulin. J. Med. Chem.41(13), 2333–2338.
Chen, Z., Liu, Y., Yang, S., Song, B., Xu, G., Bhadury, P. S., and Zhou, X. (2008). Studies on the chemical constituents and anticancer activity of Saxifraga stolonifera (L) Meeb. Bioorg. Med. Chem., 16, 1337–1344.
Cheng, A. C., Huang, T. C., Lai, C. S., & Pan, M. H. (2005). Induction of apoptosis by luteolin through cleavage of Bcl-2 family in human leukemia HL-60 cells. Eur. J. Pharmacol. 509(1), 1–10.
Choi, E. J., & Ahn, W. S. (2008). Kaempferol induced the apoptosis via cell cycle arrest in human breast cancer MDA-MB-453 cells. Nutr Res Pract, 2(4), 322–5.
Chowdhury, S. A. L. I., Kishino, K., & Satoh, R. I. E. (2005). Activity of Stilbenes and Flavonoids. Anticancer Res., 2064, 2055–2063.
Chung, H. S., Chang, L. C., Lee, S. K., Shamon, L. A., Breemen, R. B. Van, Mehta, R. G., and Kinghorn, A. D. (1999). Flavonoid Constituents of Chorizanthe diffusa with Potential Cancer Chemopreventive Activity. J. Agric. Food Chem., 36–41.
Cragg, G. M., & Newman, D. J. (2005). Plants as a source of anti-cancer agents, J. Ethnopharmacol., 100, 72–79.
De Leo, M., Braca, A., Sanogo, R., Cardile, V., DeTommasi, N., & Russo, A. (2006). Antiproliferative activity of Pteleopsis suberosa leaf extract and its flavonoid components in human prostate carcinoma cells. Planta Med, 72 (7), 604–610.

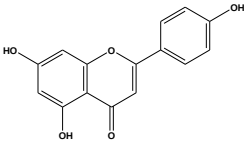
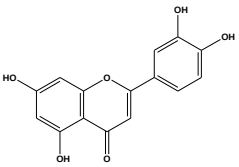
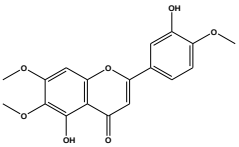
Dai, Z., Lu, W., Gao, J., Kang, H., Ma, Y., Wu, W. (2013). Anti-angiogenic effect of the total flavonoids in in Scutellaria barbata D. Don. BMC Complement Altern Med.1(13),150.
Fang, S.C. Hsu C.L., Lin H.T. and Yen G.C. (2010). Anticancer Effects of Flavonoid Derivatives Isolated from Millettia reticulata Benth in SK-Hep-1 Human Hepatocellular Carcinoma Cells, J Agric Food Chem., 58(2), 814–820.
Ferreira, J. F. S., Luthria, D. L., Sasaki, T., & Heyerick, A. (2010). Flavonoids from Artemisia annua L. as Antioxidants and Their Potential Synergism with Artemisinin against Malaria and Cancer. Molecules, 15, 3135–3170.
Ghasemzadeh, A., and Jaafar, H. Z. E. (2013). Profiling of phenolic compounds and their antioxidant and anticancer activities in pandan (Pandanus amaryllifolius Roxb .) extracts from different locations of Malaysia. BMC Complement Altern Med. 13(341), 1-9.
Haïdara, K., Zamir, L., Shi, Q. W., and Batist, G. (2006). The flavonoid Casticin has multiple mechanisms of tumor cytotoxicity action. Cancer Lett., 242(2), 180–190.
Huang, Y.T. , Jwang, J.J., Lee, P. P. , Ke, F.C., Huang, J.H., Huang, C.J., Kandaswami, C., Middleton E., and Lee M.T. (1999). Effects of luteolin and quercetin, inhibitors of tyrosine kinase, on cell growth and metastasis-associated properties in A431 cells oversxpressing epidermal growth factor receptor. Br J Pharmacol., 128(5), 999–1010.
Ikezoe, T., Chen, S. S., Heber, D., Taguchi, H., and Koeffler, H. P. (2001). Baicalin is a major component of PC-SPES which inhibits the proliferation of human cancer cells via apoptosis and cell cycle arrest. Prostate., 49(4):285-92
Kato, A., Hashimoto, Y. and Kidokor (1979). (+)-Nortrachelogenin, A New Pharmacologically Active Lignan From Wikstroemia indica. J. Nat. Prod., 44(5), 530–535.
Kanadaswami, C., Lee, L. T., Lee, P. P. H., Hwang, J. J., Ke, F. C., Huang, Y. T., & Lee, M. T. (2005). The antitumor activities of flavonoids. In Vivo, 19(5), 895–910.
Kandaswami, C., Perkins, E., Soloniuk, D. S., Drzewiecki, G., and Middleton, E. (1993). Ascorbic acid-enhanced antiproliferative effect of flavonoids on squamous cell carcinoma in vitro. Anticancer Drugs, 4(1):91-6
Kang, G. Y., Lee, E. R., Kim, J. H., Jung, J. W., Lim, J., Kim, S. K., Cho S.G., Kim, K. P. (2009). Downregulation of PLK-1 expression in kaempferol-induced apoptosis of MCF-7 cells. Eur J Pharmacol, 611(1–3), 17–21.

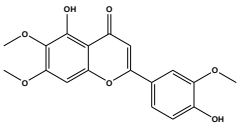
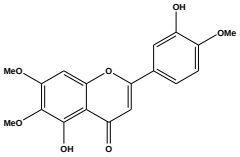
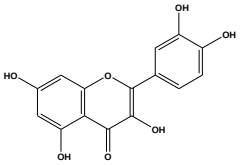
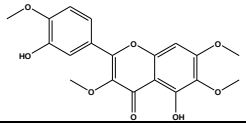
Kaufman, P. B., Duke, J. A., Brielmann, H., Boik, J., and Hoyt, J. E. (1997). A Comparative Survey of Leguminous Plants as Sources of the Isoflavones, Genistein and Daidzein: Implications for Human Nutrition and Health. J Altern Complement Med., 3(1), 7–12.
Khoo, H. E., Azian, A., Tang, S.T., and Lim, S.M. (2017). Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res., 61(1), 1361779.
Kobayakawa, J., Sato-Nishimori, F., Moriyasu, M., and Matsukawa, Y. (2004). G2-M arrest and antimitotic activity mediated by casticin, a flavonoid isolated from Viticis Fructus (Vitex rotundifolia Linne fil.). Cancer Lett., 208(1), 59–64.
Lee, D., Park, K., Park, H., Kang, S., Nagappan, A., Kim, J., Kim, E., Lee, W., Hah, Y. Chung, H., An, S., Kim, G. (2012). Flavonoids Isolated from Korea Citrus aurantium L . Induce G2 / M Phase Arrest and Apoptosis in Human Gastric Cancer AGS Cells, Evid.-Based Complementary Altern. Med., 2012, 515901, 1-11.
Lee, H. J., Lee, H. J., Lee, E. O., Ko, S. G., Bae, H. S., Kim, C. H., Ahn, K.S., Lu, J., Kim, S. H. (2008). Mitochondria-cytochrome C-caspase-9 cascade mediates isorhamnetin-induced apoptosis. Cancer Lett., 270(2), 342–353.
Lee, K., Hyun Lee, D., Jung, Y. J., Shin, S. Y., Lee, Y. H. (2016). The natural flavone eupatorin induces cell cycle arrest at the G2/M phase and apoptosis in HeLa cells. Appl. Biol. Chem., 59(2), 193–199.
Leung, H. W. C., Lin, C. J., Hour, M. J., Yang, W. H., Wang, M. Y., Lee, H. Z. (2007). Kaempferol induces apoptosis in human lung non-small carcinoma cells accompanied by an induction of antioxidant enzymes. Food Chem. Toxicol., 45(10), 2005–2013.
Levin, E. R. (2015). Integration of the Extranuclear and Nuclear Actions of Estrogen. Mol. Endocrinol., 19(8), 1951–1959.
Levy, J., Teuerstein, I., Marbach, M., Radian, S., Sharoni, Y. (1984). Tyrosine protein kinase activity in the DMBA-induced rat mammary tumor: Inhibition by quercetin. Biochem. Bioph. Res. Co., 123(3), 1227–1233.
Li, S., Pan, M. H., Lai, C. S., Lo, C. Y., Dushenkov, S., Ho, C. T. (2007). Isolation and syntheses of polymethoxyflavones and hydroxylated polymethoxyflavones as inhibitors of HL-60 cell lines. Bioorg. Med. Chem., 15(10), 3381–3389.
Li, Y., Gan, G., Zhang, H., Wu, H., Li, C., Huang, Y., Liu, Y., Liu, J. (2007). A flavonoid glycoside isolated from Smilax china L . rhizome in vitro anticancer effects on human cancer cell lines. J. Ethnopharmacol., 113, 115–124.
Li, Z. dong, Hu, X. wen, Wang, Y. tian, Fang, J. (2009). Apigenin inhibits proliferation of ovarian cancer A2780 cells through Id1. FEBS Letters, 583(12), 1999–2003.
Lin, Y., Shi, R., Wang, X., Shen, H. (2008). Luteolin , a Flavonoid with Potential for Cancer Prevention and Therapy. Curr. Cancer Drug Tar., 8, 634–646.
Lotito, S. B., Frei, B. (2006). Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans : Cause, consequence, or epiphenomenon?. Free Radic. Biol. Med., 41, 1727–1746.
Luo, H., Rankin, G. O., Liu, L., Daddysman, M. K., Jiang, B. H., Chen, Y. C. (2009). Kaempferol inhibits angiogenesis and VEGF expression through both HIF dependent and independent pathways in human ovarian cancer cells. Nutr. Cancer, 61(4), 554–563.
Ma, G., Yang, C., Qu, Y., Wei, H., Zhang, T., Zhang, N. (2007). The flavonoid component isorhamnetin in vitro inhibits proliferation and induces apoptosis in Eca-109 cells. Chem-Biol Interact, 167(2), 153–160.
Mizushina, Y., Ikuta, A., Endoh, K., Oshige, M., Kasai, N., Kamiya, K., Sataka, T.,Takazawa, H., Morita, H., Tomiyasu, H., Yoshida, H., Sugawara, F., Sakaguchi, K. (2003). Inhibition of DNA polymerases and DNA topoisomerase II by triterpenes produced by plant callus. Biochem. Bioph. Res. Co., 305, 365–373.

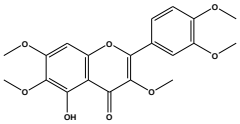
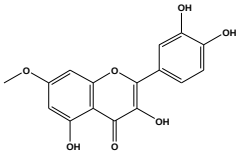
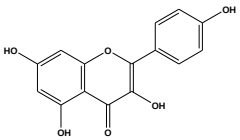
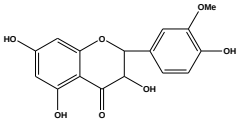
Mori, A., Nishino, C., Enoki, N., Tawata, S. (1988). Cytotoxicity of plant flavonoids against HeLa cells, Phytochemistry, 27(4), 1017-1020.
Mukhtar, H., Ahmad, N. (2000). Tea polyphenols: Prevention of cancer and optimizing health. Am. J. Clin. Nutr., 71(6), 1698–1702.
Multiethnic, T., Study, C. (2007). Flavonols and Pancreatic Cancer Risk: The Multiethnic Cohort Study, Am. J. Epidemiol.,166(8), 924–931.
Mutoh, M., Takahashi, M., Fukuda, K., Matsushima-Hibiya, Y., Mutoh, H., Sugimura, T., Wakabayashi, K. (2000). Suppression of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells by chemopreventive agents with a resorcin-type structure. Carcinogenesis, 21(5), 959–63.
Manthey, J., Guthrie, N. (2002). Antiproliferative activities of Citrus flavonoids against six human cancer cell lines. J. Agric. Food Chem., 50, 5837.
Nagao, T., Abe, F., Kinjo, J., Okabe, H. (2002). Antiproliferative Constituents in Plants 10. Flavones from the Leaves of Lantana montevidensis BRIQ. and Consideration of Structure–Activity Relationship. Biol. Pharm. Bull., 25(7), 875–879.
Ono, M., Yanaka, T., Yamamoto, M., Ito, Y., Nohara, T. (2002). New diterpenes and norditerpenes from the fruits of Vitex rotundifolia. J. Nat. Prod., 65(4), 537–541.
Parajuli, P., Joshee, N., Rimando, A., Mittal, S., Yadav, A. (2009). In vitro Antitumor Mechanisms of Various Scutellaria Extracts and Constituent Flavonoids. Planta Med, 75(1), 41–48.
Peng, J., Fan, G., Wu, Y. (2006). Preparative isolation of four new and two known flavonoids from the leaf of *Patrinia villosa Juss* by counter-current chromatography and evaluation of their anticancer activities in vitro. J. Chromatogr. A, 1115, 103–111.
Pettit, G. R., Hoard, M. S., Doubek, D. L., Schmidt, J. M., Pettit, K., Tackett, L. P., Chapuis, J.-C. (1996). Antineoplastic agents 338. The cancer cell growth inhibitory. Constituents of Terminalia arjuna (Combretaceae). J. Ethnopharmacol., 53, 57–63.
Ranelletti, F. O., Ricci, R., Larocca, L. M., Maggiano, N., Capelli, A., Scambia, G., Benedetti-Panici, P., Mancusa, S., Rumi, C., Piantelli, M. (1992). Growth inhibitory effect of Quercetin and presense of type II estrogen binding sites in human colon-cancer cell lines and primary colorectal tumours. Int. J. Cancer, 50(3), 486–492.
Raza, K., Thotakura, N., Kumar, P., Joshi, M., Bhushan, S., Bhatia, A., ... & Katare, O. P. (2015). C60-fullerenes for delivery of docetaxel to breast cancer cells: a promising approach for enhanced efficacy and better pharmacokinetic profile. *International journal of pharmaceutics*, *495*(1), 551-559.
Rodgers, E. H., Grant, M. H. (1998). The effect of the flavonoids, quercetin, myricetin and epicatechin on the growth and enzyme activities of MCF7 human breast cancer cells. Chem-Biol Interact, 116(3), 213–228.
Ruidavets, J., Teissedre, P., Ferrieres, J., Carando, S., Bougard, G., Cabanis, J. (2000). Catechin in the Mediterranean diet : vegetable , fruit or wine ?, Atherosclerosis, 153(1), 107–117.
Salmela, A. L., Pouwels, J., Kukkonen-Macchi, A., Waris, S., Toivonen, P., Jaakkola, K., Maki-Jouppila, J., Kallio, L., Kallio, M. J. (2012). The flavonoid eupatorin inactivates the mitotic checkpoint leading to polyploidy and apoptosis. Exp. Cell Res., 318(5), 578–592.
Samanta, A., Das, G., Das, S. K. (2011). Roles of flavonoids in Plants. Int J Pharm Sci Tech, 6(1), 11-35.
Sarkar, F. H., & Li, Y. (2002). Mechanisms of cancer chemoprevention by soy isoflavone genistein. Cancer Metastasis Rev., 21(3–4), 265–80.
Scambia, G., Ranelletti, F. O., Benedetti Panici, P., Bonanno, G., De Vincenzo, R., Piantelli, M., & Mancuso, S. (1990). Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. Anti-Cancer Drugs, 1(1), 45-48

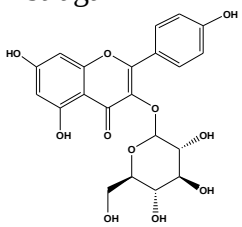
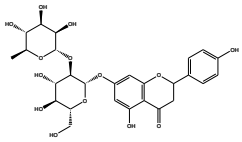
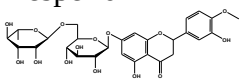
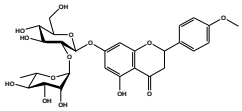
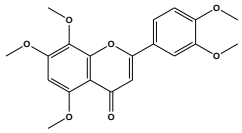
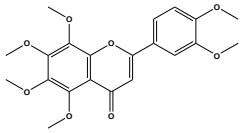
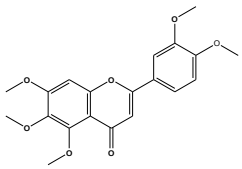
Kaur, G., Stevenson, M., Sebers, S., Worland, P., Sedlacek, H., Naik, R., Sausville, E.(1992). Growth Inhibition With Reversible Cell Cycle Arrest of Carcinoma Cells by Flavone L86-8275, J Natl Cancer I., 84(22), 1736–1740.
Shashank, K., Pandey, A. K. (2013). Chemistry and biological activities of flavonoids. The Scientific World Journal, 2013(12), 533–548.
Sheng, X., Sun, Y., Yin, Y., Chen, T., Xu, Q. (2008). Cirsilineol inhibits proliferation of cancer cells by inducing apoptosis via mitochondrial pathway. J Pharm Pharmacol, 60(11), 1523–1529.
Shi, Z. M., Wang, X. F., Qian, X., Tao, T., Wang, L., Chen, Q. D., Wang, L., Zhang, J.,Jiang, T., Kang, C., Jiang, B., Liu, N., You, Y. P. (2013). MiRNA-181b suppresses IGF-1R and functions as a tumor suppressor gene in gliomas. Rna, 19(4), 552–560.
Si, D., Wang, Y., Zhou, Y., Guo, Y., Wang, J., Zhou, H., Li, Z., Fawcett, J. (2009). Mechanism of CYP2C9 Inhibition by Flavones and Flavonols. Drug Metab Dispos, 37(3), 629–634.
So, F. V., Guthrie, N., Chambers, A. F., Caroll, K. K. (1997). Inhibition of proliferation of estrogen receptor-positive MCF-7 human breast cancer cells by flavonoids in the presence and absence of excess estrogen. Cancer Lett., 112(2), 127–133.
Surget, S., Bourdon, J. (2014). Uncovering the role of p53 splice variants in human malignancy : a clinical perspective. Onco Targets Ther, 7, 57–68.
Taniguchi, S., Fujiki, H., Kobayashi, H., Go, H., Miyado, K., Sadano, H., Shimokawa, R. (1992). Effect of (-)-epigallocatechin gallate, the main constituent of green tea, on lung metastasis with mouse B16 melanoma cell lines. Cancer Lett., 65(1), 51–54.
Herrmann, K., (1976). Flavonols and flavones in food plants: a review. , J. Fd Technol, 11, 433–448.
Teng, B. song, Lu, Y. H., Wang, Z. T., Tao, X. Y., Wei, D. Z. (2006). In vitro anti-tumor activity of isorhamnetin isolated from Hippophae rhamnoides L. against BEL-7402 cells. Pharmacol Res, 54(3), 186–194.
Yasuhiro, T., Pavlos, S, Arjun, H. B., Suresh, A., Kim, Q. T., Ikuo, S., Shigetoshi, K. (2000). Constituents of Vietnamese Medicinal Plant Orthosiphon stamineus. Chem. Pharm. Bull., 48(11), 1711–1719.
Thompson, L. U., Boucher, B. A., Liu, Z., Cotterchio, M., Thompson, L. U., Boucher, B. A., Kreiger, N. (2009). Phytoestrogen Content of Foods Consumed in Canada, Including Isoflavones, Lignans, and Coumestan, Nutr. Cancer, 54(2), 184-201.
Tseng, T.H., Chien, M.H., Lin, W.L., Wen, Y.C., Chow, J.M., Chen, C.K., Kuo, T.C., Lee, W.J. (2017). Inhibition of MDA-MB-231 Breast Cancer Cell Proliferation and Tumor Growth by Apigenin Through Induction of G2/M Arrest and Histone H3 Acetylation-mediated p21WAF1/CIP1 Expression. Environ. Toxicol., 32(2), 434–444.
Wen, L., Wu, D., Jiang, Y., Prasad, K. N., Lin, S. (2013). Identification of flavonoids in litchi (Litchi chinensis Sonn .) leaf and evaluation of anticancer activities. J. Funct. Foods, 6, 555–563.
Wenzel, U., Herzog, A., Kuntz, S., & Daniel, H. (2004). Protein expression profiling identifies molecular targets of quercetin as a major dietary flavonoid in human colon cancer cells. Proteomics, 4(7), 2160–2174.
Woerdenbag, H. J., Merfort, I., Pabreiter, C. M., Schmidt, T. J., Willuhn G., Uden,W., Pras, N., Kampinga H. H., Konings, A. W. (1994). Cytotoxicity of flavanoids and sesquiterpene lactones from Arnica species against the GLC4 and COLO 320 cell lines. Planta Med, 60, 434–437.
Yan, X., Qi, M., Li, P., Zhan, Y., Shao, H. (2017). Apigenin in cancer therapy: anti-cancer effects and mechanisms of action. Cell Biosci., 7(1), 50.
Zhang, Y., Chen, A. Y., Li, M., Chen, C., Yao, Q. (2008). Ginkgo biloba Extract Kaempferol

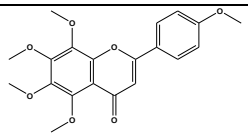
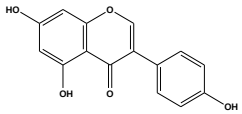
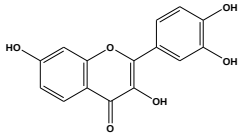
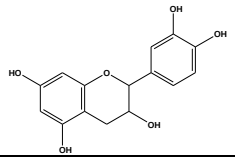
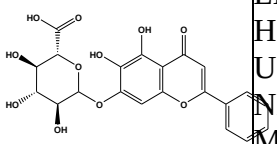
Inhibits Cell Proliferation and Induces Apoptosis in Pancreatic Cancer Cells. J. Surg. Res., 148(1), 17–23.

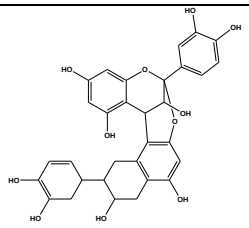
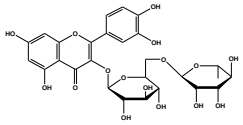
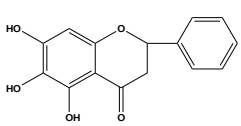
S.no.	Compound	Cell lines	Type of cancer	Mode of action	ref.
1.	Apigenin 	A2780 S2-013, CD18 U87-MG, U373-MG NHA MDA-MB-231 HMEC U-251 PC3	Human ovarian Human pancreatic glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma Prostate carcinoma	ATF3/Id1 pathway. Downregulates the GLUT1 mRNA via P13K/Akt pathway. Blockes the activation of c-MET signalling. G2/M phase cell cycle arrest. P13K/Akt Dec. Bcl-2 and Bcl-X (L).	(Yan et al., 2017) (Z. dong Li, Hu, Wang, & Fang, 2009)(Tseng et al., 2017)(Shi et al., 2013)
2.	Luteolin 	HepG2 A431 MCF-7 MiaPaCa-2 HL-60 HeLa 3P388 OVRAC3 SF-295 A498 NCI-H460 KM20-L2 SK-MEL5	Human hepatic Human skin Human breast Human pancreatic Human promyelocytic leukemia Human cervical carcinoma Human leukemia Human ovary Human brain Human renal Human lung Human colon Human melanoma	Inhibit protein phosphorylation, DNA fragmentation, inhibit tyrosine kinase, effects mitochondrial pathway and induce apoptosis.	(Huang, 1999) (Cheng, Huang, Lai, & Pan, 2005) (Wen, Wu, Jiang, Prasad, & Lin, 2013)(Pettit et al., 1996)
3.	Eupatorin 	B16F10 26-L5 MDA-MB-468, MCF-7 MCF-10A HeLa	Murine melanoma Murine colon Human breast non-transformed mammary epithelial cell line Human cervical carcinoma	Induce CYP1 enzyme Cleavage of PARP.	(Nagao, Abe, Kinjo, & Okabe, 2002) (Tezuka Yasuhiro, Stampoulis Pavlos, 2000) (V. Androutsopoulos, Arroo, Hall, Surichan, & Potter, 2008) (V. P. Androutsopoulos

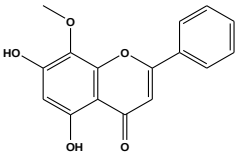
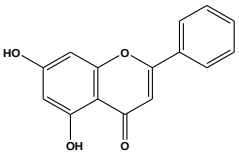
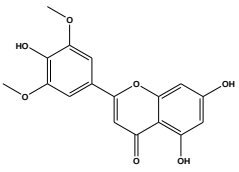
					et al., 2009) (Salmela et al., 2012)
4.	Cirsilineol 	MK-1 B16F10 Caov-3,Skov-3 PC3 HeLa HepG2	Human gastric Murine melanoma Human ovarian Human prostate Human uterus Human hepatic	Induce apoptosis via mitochondrial pathway	(Nagao et al., 2002) (Sheng et al., 2008)
5.	Eupatin 	NCI-60	60 cell lines	Inhibit tubulin polymerization.	(Beutler et al., 1998)
6.	Quercetin 	MCF-7 HT-29, COLO 201, LS-174T, WiDr OVCA433 HSC-2 HL-60 DLD-1 BGC-823	Human breast Human colon Human ovarian Squamous cell carcinoma Promyelocytic leukaemia Human colon Human gastric carcinoma	Inhibits protein kinase, RNA and DNA. Apoptosis, reverse inhibition of cell proliferation. Induce internucleosomal DNA fragmentation Induce apoptosis.	(Guthrie, Chambers, & Caroll, 1997) (Wenzel et al., 2004), (Ranelletti et al., 1992) (Scambia et al., 1990) (Chowdhury, Kishino, & Satoh, 2005) (Chen et al., 2008)
7.	Quercetagetin 6,7,3'4' tetramethyl ether	P-388 A-549 MCF-7 HT-29 KB	Murine lymphocytic leukaemia Human lung carcinoma Human breast Human colon Human nasopharynx	-	(Zheng, 1994)
8.	Casticin 	PC-12 HCT-116 KB MCF-7	Human lung Human colon Human epidermoid carcinoma Human Breast	Disrupts mitotic spindle Cell cycle arrest in G2/M.	(Ono, Yanaka, Yamamoto, Ito, & Nohara, 2002),(Ferreira et al., 2010)

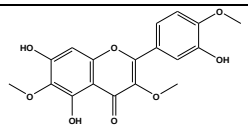
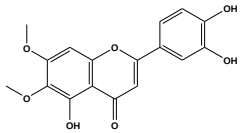
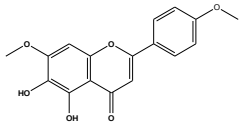
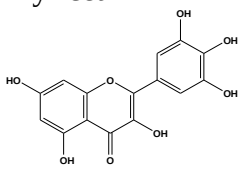
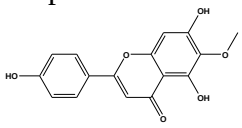
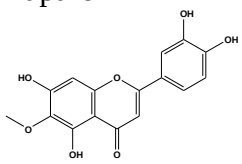
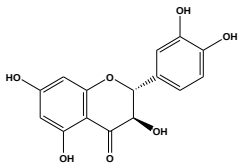
					(Kobayakawa, Sato-Nishimori, Moriyasu, & Matsukawa, 2004) (Haïdara, Zamir, Shi, & Batist, 2006)
9.	Artemetin 	HL-60	Promyelocytic leukaemia	Proaptotic activity	(S. Li et al., 2007)
10.	Chrysosplenol-D	KB HeLa tsFT210	Human epidermoid Human cervical Mouse cdc2 mutant	Inhibits phospholipid corporation of TPA stimulated Pi.	(Arisawa et al., 1991) (Arisawa & Shimizu, 1995)
11.	Rhamnetin 	HeLa DLD-1 MDA-MB-435 MCF-7 DU-145 HT-29 DMS-114 SKMEL-5	Human cervical Human colon Human breast Human breast Androgen receptor negative prostate Human colon Human lung Human melanoma	Suppress COX-2 transcription G2/M cell cycle arrest	(Mori, Nishino, Enoki, & Tawata, 1988) (Mutoh et al., 2000) (N, 2002)
12.	Kaempferol 	OVCAR-3, A2780/CP70 MCF-7,MDA-MB-453 MIA PaCa-2, Panc-1 PC-3 H-460	Ovarian cancer Human breast Pancreatic Prostate Lung non-small cell	Angiogenesis Apoptosis G2/M cell cycle arrest and apoptosis Stimulate GM-SCF production.	(Luo et al., 2009) (Kang et al., 2009),(Choi & Ahn, 2008) (Zhang, Chen, Li, Chen, & Yao, 2008) (Bandyopadhyay, Romero, & Chattopadhyay, 2008) (Leung et al., 2007)
13.	Isorhemnetin 	BEL-7402 Eca-109 LLC	Human hepatocellular Human oesophageal squamous Lewis lung cancer	Apoptosis. Inhibit proliferation and induce apoptosis. Caspase mediated apoptosis.	(Teng, Lu, Wang, Tao, & Wei, 2006) (Ma et al., 2007) (H. J. Lee et al.,

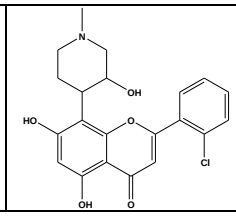
					2008)
14.	Astragalin 	DU-145 GLC-4 COLO 320	Human prostate Human small cell lung carcinoma Human colon	Caspase mediated apoptosis.	(De Leo et al., 2006) (Woerdenbag, Merfort, Pabreiter, & Al, 1994)
15.	Naringin 	AGS MCF-7	Human gastric Human breast	Inhibits progression of cell cycle in G2/M phase Apoptosis	(D. Lee et al., 2012) (Ghasemzadeh & Jaafar, 2013)
16.	Hesperidin 	AGS	Human gastric	Inhibits progression of cell cycle in G2/M phase	(D. Lee et al., 2012)
17.	Poncirin 	AGS	Human gastric	Inhibits progression of cell cycle in G2/M phase	(D. Lee et al., 2012)
18.	Isosinensetin 	AGS	Human gastric	Inhibits progression of cell cycle in G2/M phase	(D. Lee et al., 2012)
19.	Nobiletin 	AGS MDA-MB-435 MCF-7 DU-145 HT-29 DMS-114 SKMEL-5 HL-60	Human gastric Human breast Human breast Androgen receptor negative prostate Human colon Human lung Human melanoma Human leukaemia	G2/M cycle arrest	(D. Lee et al., 2012) (N, 2002) (S. Li et al., 2007)
20.	Sinensetin 	AGS	Human gastric	G2/M cycle arrest	(D. Lee et al., 2012)
21.	Tangeretin	AGS HL-60	Human gastric Human Leukaemia	Induce apoptosis.	(D. Lee et al., 2012)

					(S. Li et al., 2007), (Taniguchi et al., 1992)
22.	Genistein 	HL-60, K-562 A431 MDA-MB-231, MDA-MB-435, MCF-7 PC3, LNCaP H-460,H322 HN4 SK-Hep-1	Human leukaemia Human epidermoid Human Breast Human prostate Non small lung cell Head and neck squamous Human hepatocellular carcinoma	Inhibits PTK Inhibit EGFR tyrosine kinase G2/M cell cycle arrest, apoptosis, metastasis. G2/M cell cycle arrest, apoptosis G2/M cell cycle arrest, apoptosis Apoptosis via fia and mitochondria mediated pathways.	(Kanadaswami et al., 2005) (Sarkar & Li, 2002) (Ang, Su, In, & En, 2010)
23.	5,8,3',4',5'-pentahydroxy-3,7-dimethoxyflavone	HL-60	Human leukaemia	Inhibit TPA	(Chung et al., 1999)
24.	3''-*O*-Acetyquercitrin	HL-60	Human leukaemia	Inhibit TPA	
25.	Fistein 	HTB43	Squamous cell carcinoma	-	(Kandaswami, Perkins, Soloniuk, Drzewiecki, & Middleton, 1993)
26.	Catechin 	B16 A431 MCF-7	Mouse Melanoma Human epidermoid	Inhibits the metastasis Cell cycle arrest and apoptosis	(Taniguchi et al., 1992) (Mukhtar & Ahmad, 2000)
27.	Baicalin 	PC3, LNCaP HL-60 U87-MG NHA MDA-MB-231 HMEC U-251	Human prostate Human leukaemia glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma	Cell cycle arrest and apoptosis -	(Ikezoe, Chen, Heber, Taguchi, & Koeffler, 2001) (Paper, 2009)
28.	Procyanidine A_2	HepG2 HeLa	Human hepatoma Human cervical carcinoma	-	(Wen et al., 2013)

					
29.	Rutin 	MCF-7	Human breast	Apoptosis	(Ghasemzadeh & Jaafar, 2013)
30.	(2*S*)-5,7,2_,6_-tetrahydroxy-6,8-di (γ,γ-dimethylallyl) flavanone	A549 BEL-7402 HT-29 MCF-7 SGC-7901 k-562 A498	human alveolar basal epithelial human hepatocellular human colon human breast human Gastric human leukaemia human kidney	-	(Peng, Fan, & Wu, 2006)
31.	(2*S*)-5,7,2',6'-tetrahydroxy-6-lavandulylated flavanone	A549 BEL-7402 HT-29 MCF-7 SGC-7901 k-562 A498	human alveolar basal epithelial human hepatocellular human colon human breast human Gastric human leukaemia human kidney	-	(Peng et al., 2006)
32.	(2*S*)-5,7,2',6'-tetrahydroxy-4'-lavandulylated flavanone	A549 BEL-7402 HT-29 MCF-7 SGC-7901 k-562 A498	human alveolar basal epithelial human hepatocellular human colon human breast human Gastric human leukaemia human kidney	-	(Peng et al., 2006)
33.	Bacalein 	U87-MG NHA MDA-MB-231 HMEC U-251 PC3	glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma Prostate carcinoma	G2/M cell cycle arrest and apoptosis.	(Paper, 2009)

34.	Wogonin 	U87-MG NHA MDA-MB-231 HMEC U-251 PC3	glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma Prostate carcinoma	G2/M cell cycle arrest and apoptosis.	(Paper, 2009)
35.	Chrysin 	U87-MG NHA MDA-MB-231 HMEC U-251 PC3	glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma Prostate carcinoma	G2/M cell cycle arrest and apoptosis.	(Paper, 2009)
36.	Scuttelarein	U87-MG NHA MDA-MB-231 HMEC U-251 PC3	glioblastoma astrocytoma Human astrocytes Human breast Human mammary epithelial Malignant glioma Prostate carcinoma	G2/M cell cycle arrest and apoptosis.	(Paper, 2009)
37.	kaempferol-7-*O*-β-d-glucoside	A37 HL-60 HeLa 95-D A431 BEL-7402 MKN-45 HFL-1	Human skin malignant Human leukemia Human cervical carcinoma Human lung Human epidermoid Hepatocellular carcinoma Human gastric Human lung	G2/M and G1/S cell cycle arrest.	(Y. Li et al., 2007)
38.	Tricin 	P-388	Lymphocytic leukaemia	-	(Indica, 1981)
39.	Kaempferol-3-O-β-D-glucopyranoside	P-388	Lymphocytic leukaemia		(Indica, 1981)
40.	Centaureidin	NCI	60 cell lines	Inhibit tubulin polymerization	(Pettit et al., 1996),(Beutler et al., 1993)

					
41.	Cirsiliol 	MCF-7	Human breast	Induce CYP1A1 and CYP1B1 enzyme of mRNA.	(V.P. Androutsopoulos et al., 2009)
42.	Ladanein 	26-L5	Murine colon	-	(Tezuka Yasuhiro, Stampoulis Pavlos, 2000)
43.	6-hydroxy-5,6,4’ -trimethoxy flavone	26-L5	Murine colon	-	(Tezuka Yasuhiro, Stampoulis Pavlos, 2000)
44.	Myricetin 	MCF-7	Human breast	Inhibit protein, RNA and DNA.	(Rodgers & Grant, 1998)
45.	Isoliqiritigenin	HSC-2 HL-60	Squamous cell carcinoma Promyelocytic leukaemia	Induce internucleosomal DNA fragmentation.	(Scambia et al., 1990), (Chen et al., 2008)
46.	Hispidulin 	GLC4 COLO-320	Human small cell lung carcinoma Human colon	-	(Woerdenbag et al., 1994)
47.	Eupafolin 	GLC4 COLO-320	Human small cell lung carcinoma Human colon	-	(Woerdenbag et al., 1994)
48.	Taxifolin 	HepG2 A431 MCF-7 MiaPaCa-2	Human hepatic Human skin Human breast Human pancreatic	Inhibit protein phosphorylation.	(Huang, 1999)
49.	Flavone L86 8275	LX 529, A549	Human lung carcinoma	Blocks cell progression at G_1	(Sebers, Worland, Sedlacek, Naik, &

		MDA- 468	Human breast	and G_2 phase	Sausville, n.d.)

Zheng, G.Q. (1994). Cytotoxic Terpenoids and Flavonoids from Artemisia annua. Planta Med., 60(1), 54-57

Table 1: Flavanoids: Structure, cancer cell target and their modes of action against cancer