1. Introduction

Today, cancer had been described as one of the deadliest diseases worldwide. It has been estimated that cancer causes about 9.9 million deaths in the year 2020 \[1\]. Cancer is a complex disease characterized by uncontrolled proliferation and development of cells in tissues forming a tumour that may potentially expand to a whole organ or systematically to other tissues called metastasis \[2\]. The severity of death due to cancer in the world every year indicated that the present standard of treatment with chemotherapeutic drugs is not enough. According to the World Health Organization (WHO), the global cancer rate could increase by half by 2020 in which majority
of the affected population will be from medium and low income countries, with lack of chemotherapeutic drugs as well as other resources [13]. As result, there is need for alternative anticancer therapeutic drugs. This has pushed researchers and scientist to search for innovative alternate source of anticancer drugs from natural source including plants [4]. Initially, plants have been used in all cultures for healing wide ranges of diseases and as well to improve well-being [5,6]. Further studies demonstrated that medicinal plants contain secondary metabolites called phytochemicals, which have a positive effect on health due to their medicinal properties. These effects of the phytochemicals are attributed to the biological properties such as anti-inflammatory, antioxidant, antimicrobial and anticancer they possessed. Today, the potential of plants as a source of anticancer agents is recorded well both in experimental findings and traditional medicine [7]. In most cases, phytochemicals have been applied directly or modified chemically to develop chemical compounds used in modern medicine which include anticancer drugs. Food and Drug Administration (FDA) inform that over 60% of the drugs used in treatment of cancer are sourced from natural resources [5].

Therefore, plant-anticancer compound has been considered as a possible option for the development of new chemotherapeutics and also to improve the affectivity of the conventional drugs [8-10]. However, these plants derived compounds present many drawbacks, such as negative side effect (toxicity), low stability and difficulties in extraction from natural source [11]. Hence, the application of phytochemicals still faces challenges and need for further research is vital. Phytochemicals are largely distributed in different parts of plants with the potential of reducing the risk of different types of diseases including cancer [12].

2. Cancer

Today, cancer had been described as one of the deadliest diseases worldwide. It has been estimated that cancer causes about 9.9 million deaths in the year 2020 [1]. Cancer is a complex disease characterized by uncontrolled proliferation and development of cells in tissues forming a tumour that may potentially expand to a whole organ or systematically to other tissues called metastasis [2]. The abnormal cell behavior due to cancer may be as a result of heredity genetics or alteration of oncogens related to cell cycle and regulation of cell death (apostasis) [13]. According to World Health Organization, the main causes behind the development of cancer include; ionization radiation, reactive oxidative species (ROS), random somatic mutation, chemical agents such as alkylating agents, and biological agents [14]. The ionization radiations such as x-rays are able to disrupt the hydrogen bond between nucleic acid thereby altering its chemical structure, which may lead to alteration in normal DNA expression regulation [15]. Infectious caused by microorganisms such as bacteria, virus and fungi have also been significantly correlated with developing cancer [16]. Virus that integrate their genetic materials into the host tissue or organ may alter normal genetic expression related to cell division or even induce oncogens that could derive into cancer development [17-19]. Conversely, bacterial infection may evoke the release of toxins with cytotoxic effect and the disruption of the tissue cell matrix. Some common examples of bacterial toxins are enteric toxins from Salmonella typhi or CagA and vacuolating toxins of Helicobacter pylori, which may induce formation of new tissue (neoplasia), cell death, and alteration in the normal cell metabolism [20,21]. Other infectious pathogens such as parasitic helminths and fungi that produce direct or toxin-mediated tubular damage are also considered as oncogenic agents [22]. Apart from genetic alteration, the main recognized tumor-inducing mechanism of biological agents is tissue inflammation as a result of cell damage and subsequent neoplasia which, if unchecked, can result in potential chronic inflammation of the affected tissues (e.g., hepatic cirrhosis by Hepatitis virus) [17,23].

Reactive oxygen species (ROS) such as hydroxyl radical or hydrogen peroxide are believed to provoke the alteration and damage of the cell membrane, DNA and lipids [24]. They are also been identified to increase in tumor cells enhancing their survivability and proliferation [25]. Nonetheless, the common factor besides possible genetic alterations by oxidative stress, infections and ultraviolet radiation is the associated inflammatory response [22,24]. On this matter, chronic inflammation is considered both cause and symptom of other ailments, but particularly of cancer, as tumorous cells secrete several pro-inflammatory molecules [26]. For example, it is well known that the pro-inflammatory mediator cyclooxygenase-2 (COX-2) is over-expressed in several types of cancer. As such, pro-inflammatory mediators are markers of cancer and could be also a possible target for anticancer therapies [27,28]. Considering chemical carcinogens aside from potentially hazardous substances, the main carcinogens originate in diet. Major chemical carcinogens include polycyclic aromatic hydrocarbons (PAHs), N-nitroso compounds, heterocyclic amines (HCAs) and alcohol. PAHs like anthracene appear in combustion reactions, and are reported in grilled or smoked foods, as well as being part of urban air pollution. They are linked to lung and digestive tract cancer [29,30]. Closely related in their
effects and occurrence, HCAs like 2-Amino-1-methyl-6-phenylimidazo [4,5-b] pyridine are the result of pyrolysis of proteins and amino acids in meat or fish foods \[51,52\]. It is worth mentioning that tobacco is reported to contain high levels of PAHs and HCAs, linking them to the pro-carcinogen effects of tobacco consumption \[33\]. N-nitroso compounds are additives in processed meats and include nitrites and nitrosamines like N-nitrosodimethylamine that have been correlated to gastric cancer development \[34\]. Ethanol as well as other alcohols present in beverages and spirits induce many metabolic and endocrine disorders along with being highly cytotoxic chemicals and attributed to cause many types of cancers \[35\]. Altogether, it should be considered that a variety of exogenous carcinogens from different sources can heavily prompt cancer development

3. Phytochemicals

The phytochemicals are secondary metabolites or chemical compound produced during metabolic process in plants which are useful in the protection of plants \[37\]. Many of these secondary metabolites possess vital medicinal properties which have many applications in pharmaceutical industries. Phytochemicals such as alkaloids, tannin, quinones, flavonoids, vitamins and amines are free radical scavenging molecules and possess antimicrobial, anti-inflammatory, antioxidant and anticancer activities \[38\]. In general, most plants bioactive components possess antioxidant property which protects human cells against oxidative damage. Phytochemical from such plants are used for reducing the intensity of inflammation related diseases and as well provide protective effect by countering reactive oxygen species (ROS) \[39\].

4. Some Phytochemicals Used as Anticancer Agents

4.1 Cyanidin

Cyanidin is an extract of pigment from red berries such as blackberry, apples, red onion, red cabbage, plums, raspberry, cranberry and grapes. The extract possesses radical scavenging and antioxidant effect which may reduce cancer risk. It is reported that cyanidin inhibits cell proliferation and gene expression in colon cancer cell \[40\]. Another research demonstrated that Cyanidin-3-glucoside (C3G) attenuated the benzo[a]pyrene-7,8-diol-9,10-epoxide-induced activation of AP-1 and NF-κB and phosphorylation of MEK, MKK4, Akt, and MAPKs and blocked the activation of the Fyn kinase signaling pathway, which may contribute to its chemo-preventive potential \[41\]. Cyanidin-3-glucoside inhibit ethanol-induced activation of ErbB2/cSrc/FAK pathway in breast cancer cells and may reduce ethanol-induced breast cancer metastasis \[42\]. inhibition of growth and induction of apoptosis in tumorigenic rat esophagus cell line \[43\], and inhibition of UVB-induced COX-2 expression and PGE2 secretion in the epidermal skin cell line by suppressing NF-κB and AP-1 which are regulated by MAPK \[44,46\].

4.2 Fisetin

Fisetin is the flanone found in several plants such as Eurasian smoke tree, apple, grape, onion, *Acacia*, cucumber, strawberry, and persimmon \[47\]. The compound has been found to reduce aging effect in fruit fly or yeast \[48\] and exert anti-inflammatory effect in LPS-induced acute pulmonary inflammation and anticarcinogenic effects in HCT-116 human colon cancer cells \[49\]. Fisetin is also a potent antioxidant and modulates lipid and protein kinase pathways. Along with other flavonoids such as luteolin, galangin, quercetin and EGCG, induced the expression of Nrf2 and the phase II gene product HO-1 in retinal pigment epithelial cells which could retinal pigment epithelial cells from death due to oxidative stress with high degree of potency and low toxicity and reduced hydrogen peroxide induced cell death. A study conducted by Khan et al. \[50\] found dual inhibition of PI3K/Akt and mTOR signaling in human non-small cell lung cancer cells by fisetin.

4.3 Genistein

Genistein is the isoflavane that originate from a number of plants such as fava beans, lupine, soy beans, coffee, *Flemingia vestita* and kudzu. Genistein functions as anthelmintic, antioxidant and as well found to have antiangiogenic effect i.e. blocking of blood vessels formation. It also found to block the uncontrolled cell growth associated with cancer most likely by inhibiting the enzyme that regulate cell survival (growth factor) and cell division. The genistein activity was actively functions as tyrosine inhibitor by inhibiting DNA topoisomerase II \[51\]. *In vivo* and *in vitro* studies show that genistein is important in treating leukemia \[52\].

4.4 Gingerol

Gingerol is an active component of fresh ginger with characteristics spiciness. It is known for its anticancer activity against cancer in the colon \[53\], ovary, breast \[54\] and pancrease \[55\]. A review recently conducted by Oyagbemi et al. \[56\] summed up the mechanisms in the medicinal effect of gingerol. In summary, gingerol has
demonstrated anti-inflammatory, antioxidant and antitumor promoting properties and decreases iNOS and TNF-alpha expression via suppression of IkBα phosphorylation and NF-κB nuclear translocation \[50\]. Treating MOLT4 and K562 with gingerol, the ROS level was significantly higher than the control, including apoptosis of leukemia cells by mitochondrial pathway.

### 4.5 Kaempferol

Kaempferol is a natural flavonol isolated from grape fruit, apples, tea, witch hazel, Brussels sprout broccoli etc. it has been studied for pancreatic cancer \[57\] and lung cancer \[58\]. Kaempferol has also been investigated for its radical scavenging effect, antiangiogenic and anticancer properties. The compound displayed moderate cytostatic activity of 24.8 - 64.7µM in the cell line of PC3, HeLa, and K562 human cancer cell. Kaempferol has been studied as aryl hydrocarbon receptor antagonist showing inhibition of ABCG2upregulation, thereby reversing the ABCG2-mediated multidrug resistance and this can be useful for treatment of esophageal cancer.

### 4.6 Lycopene

Lycopene as phytochemical is a bright red pigment from fruits such as watermelons, tomato, red papayas and red carrot. It shows antioxidant activity and chemopreventive effect in prostate cancer. The anticancer property of lycopene is largely attributed to activating cancer preventing enzymes such as phase II detoxification enzymes \[60\]. Lycopene was found inhibiting human cancer cell proliferation and suppressing insulin like growth factor-I-stimulated growth. This may open new avenue for its study on the role of the treatment and prevention of endometrial cancer and other forms of tumors. The Lycopene also possessed inhibitory effects on endometrial and breast cancer cell \[61\], prostate and colon cancer cells \[62\].

### 4.7 Quercetin

Quercetin is a flavonoid compound mostly found in leafy vegetables, berries and onions, to which the anticancer property is attributed \[63\]. In this sense, numerous studies in vivo and in vitro pre-clinical studies have shown positive results. Regarding its action mechanisms, quercetin has been demonstrated to induce cell cycle arrest by regulating cyclin D1 and p53-related pathways; apoptosis trough the induction of pro-apoptotic factors and the decrease of anti-apoptotic ones; induces autophagy and inhibits proliferation, angiogenesis and metastasis \[63\]. These effects have been observed in different in vitro cell lines, including breast, ovarian, lung and colon cancer cells, among many others \[63\], and also in different in vivo mice models \[64\]. Furthermore, quercetin has been reported to enhance the efficacy of chemotherapeutic drugs \[65\]. Regarding clinical trials, several have evaluated the suitability of quercetin as anticancer drug. For example, a study conducted on humans reported that a high intake of quercetin in the diet is inversely related to the risk of gastric adenocarcinoma \[66\]. Another study evaluated the use of quercetin to prevent and treat oral mucositis induced by chemotherapy. The results showed a significant reduction of oral mucositis incidence in the quercetin treated group, which may suggest that this compound could be used to palliate chemotherapy side-effects \[67\].

### 4.8 Resveratrol

Resveratrol is a phenolic compound present in some fruits, such as grapes, peanuts, blueberries and blackberries. Numerous studies have evaluated the anticancer properties of this compound. Several action mechanisms of resveratrol have been described: positive regulation of p53 and BAX proteins (related with pro-apoptotic pathways) and negative regulation of NF-κB, AP-1, hypoxia-inducible factor 1-alpha (HIF-1α), matrix metalloproteases, Bcl-2 protein, COX-2, cytokines and CDK \[68\]. Some pre-clinical studies performed in vitro demonstrated that resveratrol was able to suppress the cell proliferation through cell cycle arrest, induce apoptosis and modulate autophagy in different cancer cell lines, including ovarian cancer cell line, resistant human leukemia cells, non-small-cell lung cancer and human lung adenocarcinoma \[69\]. Regarding in vivo studies, the anticancer properties of these compounds were also significant. For example, in an in vivo study, resveratrol was administered to mice, leading to a 60% reduction in the appearance of sporadic colorectal cancer. Similarly, resveratrol inhibited cell proliferation, induced the apoptosis and suppressed the angiogenesis and metastasis in bladder cancer mice models \[70\]. Resveratrol has been also reported to enhance the efficacy of traditional chemotherapeutic drugs, including temozolomide, doxorubicin and paclitaxel in mice models \[71\].

### 5. Conclusions

Cancer is a complex disease that every year costs several millions of human lives. The uncontrolled proliferation of cells causes the incorrect functioning of the body, with a long list of symptoms and finally, death. So, given the health and social importance
of this disease, but also its economic impact on the health system, new therapeutic alternatives are being continuously investigated. Traditional plants have been historically considered as an endless source of new compounds for the development of new pharmaceuticals and drugs. Therefore, nowadays researchers have at their complete disposal, plenty of ethnomedicinal and ethnopharmacological information of very different plant species which is a tool for selecting candidates and lead the research to those plants more promising. In this context, a variety of phytochemicals obtained from plants have been discovered and are currently used in cancer therapies such as cyanidin, fisetin, genistein, gingerol kaempferol, quercetin, resveratrol.

References

[1] International Agency for Research on Cancer Global Cancer Observatory. Available online: https://gco.iarc.fr/today (accessed on 31 December 2020).
[2] Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, Chomienne C, Ishikawa F, Schuringa JJ, Stassi G, et al. Cancer stem cell definitions and terminology: The devil is in the details. Nat. Rev. Cancer. 2012, 12, 767-775.
[3] https://www.who.int/mediacentre/news/releases/2003/pr27/en/.
[4] Lichota A, Gwozdzinski K. Anticancer Activity of Natural Compounds from Plant and Marine Environment. Int. J. Mol. Sci. 2018, 19, 3533.
[5] Babaei G, Aliarab A, Abroon S, Rasmi Y, Aziz SGG. Application of sesquiterpene lactone: A new promising way for cancer therapy based on anticancer activity. Biomed. Pharmacother. 2018, 106, 239-246.
[6] Garcia-Oliveira P, Fraga-Corral M, Pereira AG, Lourenço-Lopes C, Jimenez-Lopez C, Prieto MA, Simal-Gandara J. Scientific basis for the industrial application of traditionally used plants of the Rosaceae family. Food Chem. 2020, 330, 127197.
[7] Lopes CM, Dourado A, Oliveira R. Phytotherapy and Nutritional Supplements on Breast Cancer. Biomed Res. Int. 2017, 1-42.
[8] Iqbal J, Abbasi BA, Mahmood T, Kanwal S, Ali B, Shah SA, Khalil AT. Plant-derived anticancer agents: A green anticancer approach. Asian Pac. J. Trop. Biomed. 2017, 7, 1129-1150.
[9] Mao QQ, Xu XY, Shang A, Gan RY, Wu DT, Atanasov AG, Li H, Bin Phytochemicals for the prevention and treatment of gastric cancer: Effects and mechanisms. Int. J. Mol. Sci. 2020, 21, 570.
[10] Redondo-Blanco S, Fernández J, Gutiérrez-del-Río I, Villar CJ, Lombó F. New insights toward colorectal cancer chemotherapy using natural bioactive compounds. Front. Pharmacol. 2017, 8, 1-22.
[11] Clardy J, Walsh C. Lessons from natural molecules. Nature 2004, 432, 829-837.
[12] Abbasi BA, Iqbal J, Ahmad R, Bibia S, Mahmooda T, Kanwal S, Bashira S, Gula F, Hameed S. Potential phytochemicals in the prevention and treatment of esophagus cancer: A green therapeutic approach Pharmacological Reports 71, 2019, 644-652 http://dx.doi.org/10.1016/j.pharep.2019.03.001.
[13] Fernald K, Kurokawa M. Evading apoptosis in cancer. Trends Cell Biol. 2013, 23, 620-633.
[14] Stewart BW, Wild CP. World Cancer Report 2014; WHO Press;World Health Organization: Geneva, Switzerland, 2014; ISBN 978-92-832-0443-5.
[15] Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int. J. Dermatol. 2010, 49, 978-986.
[16] International Agency for Research on Cancer. Biological Agents, Volume 100B: A Review on Human Carcinogens; IARC: Lyon, France, 2012.
[17] Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y, Zhao J, Liu SP, Zhuang XH, Lin C. et al. Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma. Nat. Commun. 2016, 7, 1-10.
[18] Martin D, Gutkind JS. Human tumor-associated viruses and new insights into the molecular mechanisms of cancer. Oncogene 2008, 27, S31-S42.
[19] Hansen A, Henderson S, Lagos D, Nikitenko L, Coulter E, Roberts S, Gratrix F, Plaisance K, Renne R, Bower M. et al. KSHV-encoded miRNAs target MAF to induce endothelial cell reprogramming. Genes Dev. 2010, 24, 195-205.
[20] Wen S, Moss SF. Helicobacter pylori virulence factors in gastric carcinogenesis. Cancer Lett. 2009, 282, 1-8.
[21] Scanu T, Spaapen RM, Bakker JM, Pratap CB, Wu LE, Hofland I, Broeks A, Shukla VK, Kumar M, Janssen H. et al. Salmonella Manipulation of Host Signaling Pathways Provokes Cellular Transformation Associated with Gallbladder Carcinoma. Cell Host Microbe 2015, 17, 763-774.
[22] Elsland D, Neefjes J. Bacterial infections and cancer. EMBO Rep. 2018, 19, 1-11.
[23] Mesri EA, Cesarman E, Boshoff C. Kaposi’s sarcoma and its associated herpesvirus. Nat. Rev. Cancer 2010, 10, 707-719.
[24] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic. Biol. Med. 2010, 49, 1603-1616.
[25] Moloney JN, Cotter TG. ROS signalling in the biolog-
gly of cancer. Semin. Cell Dev. Biol. 2018, 80, 50-64.
[26] Cruz SM, Balkwill FR. Inflammation and cancer: Advances and new agents. Nat. Rev. Clin. Oncol. 2015, 12, 584-596.
[27] Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, Edwards DA, Flickinger AG, Moore R.J, Seibert K. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res. 2000, 60, 1306-1311.
[28] Qu X, Tang Y, Hua S. Immunological approaches towards cancer and inflammation: A cross talk. Front. Immunol. 2018, 9.
[29] Shen H, Tao S, Liu J, Huang Y, Chen H, Li W, Zhang Y, Chen Y, Su S, Lin N. et al. Global lung cancer risk from PAH exposure highly depends on emission sources and individual susceptibility. Sci. Rep. 2014, 4, 1-8.
[30] Bansal V, Kim KH. Review of PAH contamination in food products and their health hazards. Environ. Int. 2015, 84, 26-38.
[31] Sugimura T, Wakabayashi K, Nakagama H, Nagao M. Heterocyclic amines: Mutagens/carcinogens produced during cooking of meat and fish. Gann Monogr. Cancer Res. 2004, 52, 71-96.
[32] Puangsombat K, Gadgil P, Houser TA, Hunt MC, Sugimura T, Wakabayashi K, Nakagama H, Nagao Y. The role of dietary polyaromatic hydrocarbons in lung cancer. Cancer Epigenetics. 2015, 6, 1-8.
[33] WHO Report on the Global Tobacco Epidemic, 2011: Warning About the Dangers of Tobacco, 3rd ed.; World Health Organization: Geneva, Switzerland, 2011.
[34] Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: A meta-analysis. Nutrients 2015, 7, 9872.
[35] Prad E, Rota M, Rehm J, Shield K, Zatoński W, Hashibe M, La Vecchia C, Boffetta P. Occurrence of heterocyclic amines in cooked meat products. Meat Sci. 2012, 90, 739-746.
[36] Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: A meta-analysis. Nutrients 2015, 7, 9872.
[37] Prad E, Rota M, Rehm J, Shield K, Zatoński W, Hashibe M, La Vecchia C, Boffetta P. Occurrence of heterocyclic amines in cooked meat products. Meat Sci. 2012, 90, 739-746.
[38] WHO Report on the Global Tobacco Epidemic, 2011: Warning About the Dangers of Tobacco, 3rd ed.; World Health Organization: Geneva, Switzerland, 2011.
[39] Song P, Wu L, Guan W. Dietary nitrates, nitrites, and nitrosamines intake and the risk of gastric cancer: A meta-analysis. Nutrients 2015, 7, 9872.
[40] Kim JM, Kim JS, Yoo H, Choung MG, Sung MK. Effects of black soybean [Glycine max (L.) Merr.] seed coats and its anthocyanidins on colonic inflammation and cell proliferation in vitro and in vivo. J Agric Food Chem, 2008, 56:8427-8433.
[41] Lim TG, Kwon JY, Kim J, Song NR, Lee KM, Heo YS, Lee HJ, Lee KW. Cyanidin-3-glucoside suppresses B[a]PDE-induced cyclooxygenase-2 expression by directly inhibiting Fyn kinase activity. Biochem Pharmacol 2011, 82:167-174.
[42] Xu M, Bower KA, Wang S, Frank JA, Chen G, Ding M, Wang S, Shi X, Ke Z, Luo J. Cyanidin-3-glucoside inhibits ethanol-induced invasion of breast cancer cells overexpressing ErbB2. Mol Cancer 2011, 9:285. https://doi.org/10.1186/1476-4598-9-285.
[43] Zikri NN, Ried KM, Wang LS, Lechner J, Schwartz SJ, Stoner GD. Black raspberry components inhibit proliferation, induce apoptosis, and modulate gene expression in rat esophageal epithelial cells. Nutr Cancer 2009, 61:816-826.
[44] Kim JE, Kwon JY, Seo SK, Son JE, Jung SK, Min SY, Hwang MK, Heo YS, Lee KW, Lee HJ. Cyanidin suppresses ultraviolet B-induced COX-2 expression in epidermal cells by targeting MKK4, MEK1, and Raf-1. Biochem Pharmacol 2010, 79:1473-1482.
[45] Kim YS, Milner JA. Targets for indole-3-carbinol in cancer prevention. J Nutr Biochem 2005, 16:65-73.
[46] Acharya A, Das I, Singh S, Saha T. Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogenesis. Recent Pat Food Nutr Agric 2010, 2:166-177.
[47] Maher P, Dargusch R, Ehren JL, Okada S, Sharma K, Schubert D. Fisetin lowers methylglyoxal dependent protein glycation and limits the complications of diabetes. PLoS One 2011, 6:e21226. https://doi.org/10.1371/journal.pone.0021226.
[48] Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature 2004, 430:686-689.
[49] Geraets L, Haegens A, Brauers K, Haydock JA, Vernooy JH, Wouters EF, Bast A, Hageman GJ. Inhibition of LPS-induced pulmonary inflammation by specific flavonoids. Biochem Biophys Res Commun 2009, 382:598-603.
[50] Khan N, Iqbal Z, Adhami VM, Suh Y, Mukhtar H. Dual inhibition of phosphatidylinositol 3-kinase/Akt and mammalian target of rapamycin signaling in human non small cell lung cancer cells by a dietary flavonoid fisetin. Int J Cancer 2012, 130:1695-1705.
[51] Lopez-Lazaro M, Willmore E, Austin CA. Cells lacking DNA topoisomerase II beta are resistant to genistein. J Nat Prod 2007, 70:763-767.

[52] Wang W, Bringe NA, Berhow MA, Gonzalez de Mejia E. Beta-conglycinins among sources of bioactives in hydrolysates of different soybean varieties that inhibit leukemia cells in vitro. J Agric Food Chem 2008, 56:4012-4020.

[53] Jeong CH, Bode AM, Pugliese A, Cho YY, Kim HG, Shim JH, Jeon YJ, Li H, Jiang H, Dong Z. [6]-Gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase. Cancer Res 2009, 69:5584-5591.

[54] Lee HS, Seo EY, Kang NE, Kim WK. [6]-Gingerol inhibits metastasis of MDA MB-231 human breast cancer cells. J Nutr Biochem 2008, 19:313-319.

[55] Oyagbemi AA, Saba AB, Azeez OI. Molecular targets of [6]-gingerol: its potential roles in cancer chemoprevention. Biofactors 2010, 36:169-178.

[56] Notthlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Flavonols and pancreatic cancer risk: the multiethnic cohort study. Am J Epidemiol 2007, 166:924-931.

[57] Cui Y, Morgenstern H, Greenwood S, Tashkin DP, Mao JT, Cai L, Cozen W, Mack TM, Lu QY, Zhang ZF. Dietary flavonoid intake and lung cancer: a population-based case-control study. Cancer 2008, 112:2241-2248.

[58] Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst 1995, 87:1767-1776.

[59] Nahum A, Hirsch K, Danilenko M, Watts CK, Prall OW, Levy J, Sharoni Y. Lycopene inhibition of cell cycle progression in breast and endometrial cancer cells is associated with reduction in cyclin D levels and retention of p27(Kip1) in the cyclin E-cdk2 complexes. Oncogene 2001, 20:3428-3436.

[60] Dihal AA, De Boer V, Van Der Woude H, Tilburgs C, Bruijnijts JP, Aihl GM, Rietjens I, Woutersen RA, Stierum R.H. Quercetin, but not its glycosidated conjugate rutin, inhibits azoxymethane-induced colorectal carcinogenesis in F344 rats. J. Nutr. 2006, 136, 2862-2867.

[61] Tang SM, Deng XT, Zhou J, Li QP, Ge XX, Miao L. Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. Biomed. Pharmacother. 2020, 121, 109604.

[62] Albrecht C, Cittadini MC, Soria EA. Pharmacological Activity of Quercetin and 5 caffeoylquinic Acid Oral Intake in Male Balb/c Mice with Lung Adeno-carcinoma. Arch. Med. Res. 2020, 51, 8-12.

[63] Shiote AA, Sharma N, Girm P, Khandwekar A, Baruah M, Garnaik B, Koratkar S. LHRH-conjugated, PEGylated, poly-lactide-co-glycolide nanocapsules for targeted delivery of combinational chemotherapeutic drugs Docetaxel and Quercetin for prostate cancer. Mater. Sci. Eng. C 2020, 114, 111035.

[64] Ekström AM, Serafini M, Nyrén O, Wolk A, Bosetti C, Bellocco R. Dietary quercetin intake and risk of gastric cancer: Results from a population-based study in Sweden. Ann. Oncol. 2011, 22, 438-443.

[65] Kooshyar MM, Mozafari PM, Amirchaghmaghi M, Pakfetrat A, Karoos P, Mohasel MR, Orafai H, Azarian AA. A randomized placebo-controlled double blind clinical trial of quercetin in the prevention and treatment of chemotherapy-induced oral mucositis. J. Clin. Diagnostic Res. 2017, 11, ZC46-ZC50.

[66] Czop M, Bogucka-Kocka A, Kubrak T, Knap-Czop K, Makuch-Kocka A, Galkowski D, Wawer J, Kocki T, Kocki J. Imaging flow cytometric analysis of stilbene-dependent apoptosis in drug resistant human leukemic cell lines. Molecules 2019, 24, 1896.

[67] Ganapathy S, Chen Q, Singh KP, Shankar S, Srivastava RK. Resveratrol enhances antitumor activity of TRAIL in prostate cancer xenografts through activation of FOXO transcription factor. PLoS ONE 2010, 5, 15627.

[68] Rai G, Misra S, Suman S, Shukla Y. Resveratrol improves the anticancer effects of doxorubicin in vitro and in vivo models: A mechanistic insight. Phyto-medicine 2016, 23, 233-242.