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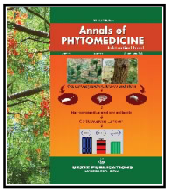

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Plant derived secondary metabolites as multiple signaling pathways inhibitors against cancer

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Abstract

Cancer is a major worldwide public health problem having complex and varied causative factors. The major obstacles for the success of precision cancer therapy are tumor heterogeneity and emergence of drug resistance. Both the challenges are being closely related leading to the therapeutic failures in clinical exercise. Targeted approach against cancer hit a single molecule expressed in neoplastic cells, thus frequently associated with development of resistance. Therefore, owing to the fact that in cancer cells, many signaling pathways operate in parallel; the idea of multitargeted therapy is suggested as a promising alternative. Natural compounds having vast chemical diversity and relatively safer with little or no side effects, thereby offer immense promise for the discovery and development of potent therapeutics against diverse human diseases including cancer. Modern drug discovery based on computational approaches has immense potential to identify novel therapeutics for multiple targets out of millions of compounds. Furthermore, these approaches allow the determination of the efficacy of each compound with its target before its mass production and biological testing. Thus, the present review describes the in-depth analysis of multitargeted phytochemicals as potent therapeutic molecules against cancer. Identification of such potential multipronged compound will strengthen drug discovery by medicinal chemists/researchers to promote understanding and collaboration with clinical scientists.

1. Introduction

Cancer is the major non-communicable diseases associated with uncontrolled cell growth. Globally, it considered second stellar reason of death, with approximately 9.6 million deaths reported in 2018 (Pereyra *et al*., 2019). In order to control the spread of the cancer both preventive as well as treatment strategies are important. Thus, in view of fact that between 30-35% of all cancers are potentially preventable, the various cancer risk factors such as tobacco, alcohol, occupational hazards, pollutants, radiation and unhealthy diets, inherited genetic mutations, hormones, immune disorders and infections are taken in to consideration as the preventive cancer strategy (De Flora and La Maestra, 2015). Similarly, based on the key characteristic features of cancer development and progression, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, energy metabolism and evading immune destruction (Hanahan and Weinberg, 2011).

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Therapeutics targeted against a single cancer specific molecule has been practicized for a long time. Thus, towards the end of the 20th century, most drugs have emerged from the concept of one-molecule-one-target-one-disease (Alcaro *et al*., 2019). This strategy was founded on the identification and optimization of small chemical entities able to recognize specifically one target, believed to be fully responsible for a particular disease. The purpose of the “one drug-one target” conceptualization was to identify bioactive metabolites/ compounds with a limited risk of off-target properties, associated with side effect of drugs. This concept started to change in the last twenty years or so due to the growing awareness that drugs designed to act on individual molecular targets are usually inadequate for multigenic diseases such as cancer, neurodegenerative, and infectious diseases (Ramsay *et al*., 2018). For the treatment of multigenic diseases “Drug-cocktails” approach is very renowned with the concerns of drug-drug interactions as well as to patients’ compliance. In parallel, molecules hitting more than one target may possess, in principle, a more efficient effect as compared to those of single-targeted ones (Zugazagoitia *et al*., 2016). This multitarget based therapeutic strategy is suggested to be a promising one in case of cancer therapeutics in view of the fact that in cancer many signaling pathways operate in parallel. Moreover, side effects exhibited by synthetic/semisynthetic anticancer drugs along with lack of selectivity, toxicity and the development of drug resistance, have limited their universal acceptability. In view of this, search for novel, safer, efficient therapeutic molecules are in demand worldwide

(Nikolaou *et al*., 2018; Nurgali *et al*., 2018). In this direction, phytochemicals, being natural, are often considered to be less toxic and relatively safer substitutes to synthetic drugs, thereby offer immense promise for the discovery and development of potent therapeutics against diverse human diseases including cancer. Thus, more than 3000 plants worldwide have been reported to possess anticancer activities (Alves-Silva *et al*., 2017) and over 60% of the approved drugs/new drug developments for cancer are from natural sources (Herranz-López *et al*., 2018). Taxenes such as paclitaxel (Taxol) and docetaxel (Taxotere), vincristine and vinblastine are the most admired plant-derived anticancer compounds those target microtubule cytoskeleton system. Other than these trastuzumab (Herceptin) and bevacizumab (Avastin) also using as chemo agents against cancer (Herranz-López*et al*., 2018). Hence, the present review covers the literature that deals with therapeutic potential of plant derived secondary metabolites (phytochemicals) as multitargeted molecules against cancer. In addition, the general description of cancer giving their hallmarks, morbidity, mortality, prevention and treatment strategies as well as computational approaches for multitargeted anticancer drug discovery have also been discussed.

1.1 Morbidity and mortality

Cancer is major public health problem, affecting people belonging to all region and socioeconomic level. According to estimates from the American Cancer Society, there were 17.0 million new cancer cases in 2018 worldwide, of which 0.6 million occurred in countries with a low HDI, 2.8 million in medium-HDI countries, 6.4 million in high-HDI countries, and 7.2 million in very high-HDI countries (American Cancer Society, 2018). Gender-wise occurrence of cancer, worldwide, is one out of 5 men and one out of 6 women (WHO, 2018a). These estimates did not include non-melanoma skin cancers, which are not tracked in cancer registries. The corresponding estimates for total cancer deaths in 2018 were 9.6 million (about 26,000 cancer deaths a day), out of which 4.0 million were from economically developed countries while those of 0.6 million from economically developing countries along with 1.8 million in medium-economically developed countries, and 3.2 million in very high-economically developed countries (American Cancer Society, 2018) .Worldwide, one out of 8 men and one out of 11 women die from the disease (WHO, 2018b). Worldwide, occurrence and death involving cancer, based on cancer types and gender, is depicted in Figure 1.

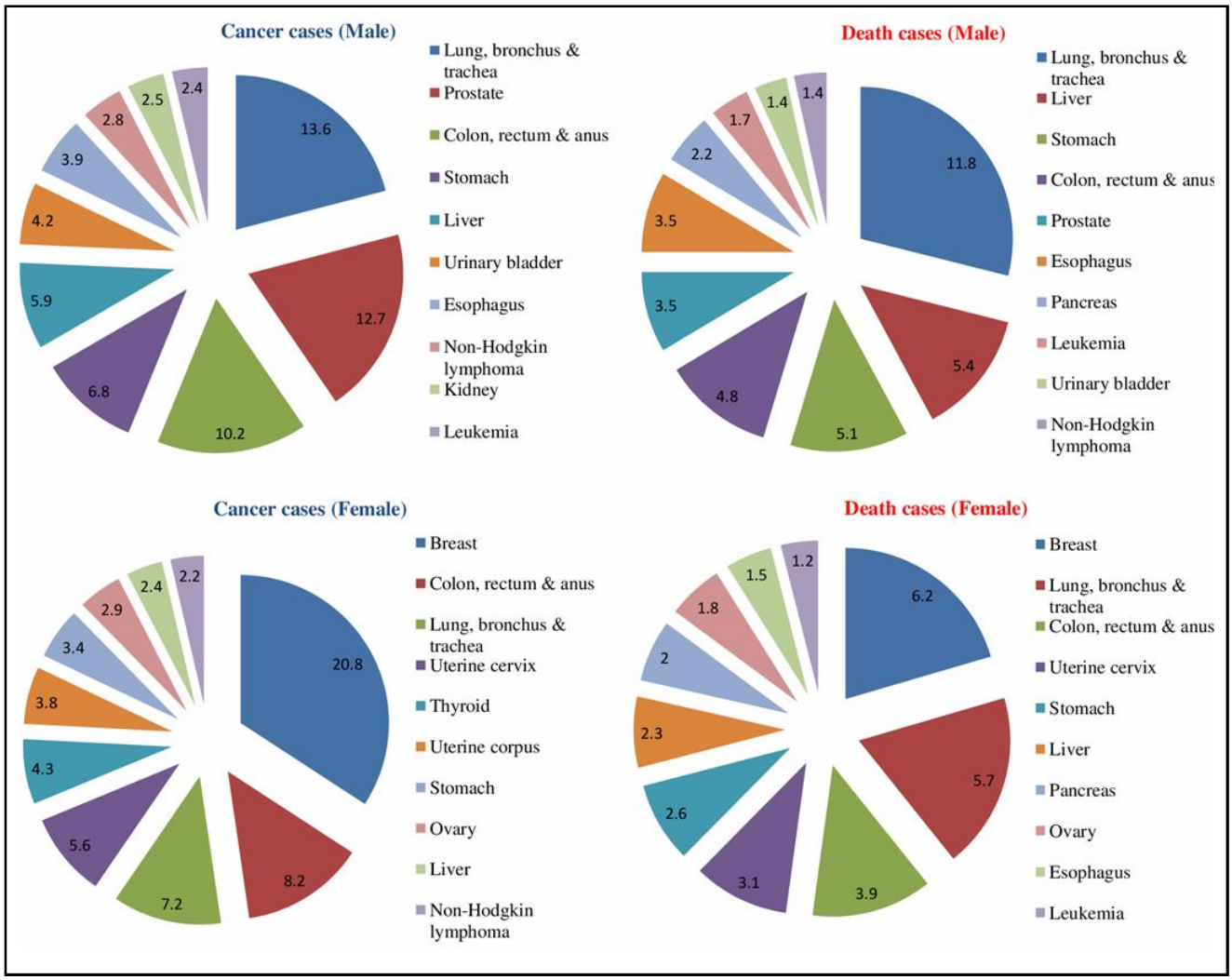

Figure 1: Worldwide, occurrence and death involving cancer, based on cancer types and gender.

1.2 Hallmarks of cancer

Hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, energy metabolism and evading immune destruction (Hanahan and Weinberg, 2011). These hallmarks of cancer have proved to be very useful in our understanding of cancer and in rational drug design (Figure 2).

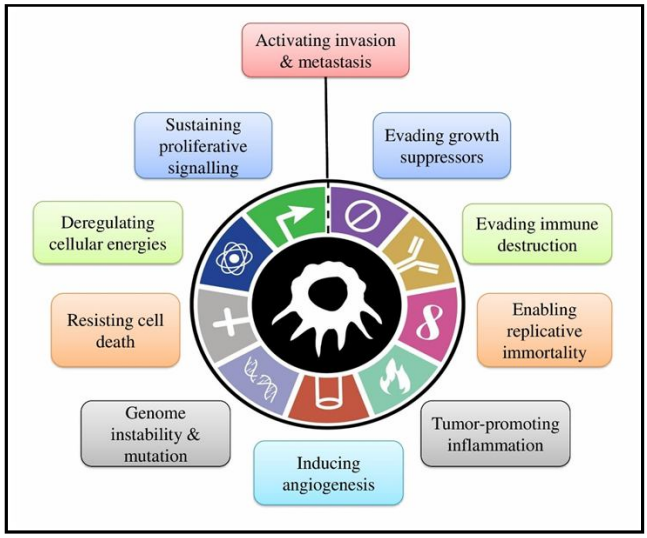

Figure 2: Hallmarks of cancer.

1.3 Strategies of cancer control

1.3.1 Treatment strategies

Cancer treatment includes various therapies to cure a cancer, shrink a cancer or stop the progression of a cancer. Based on the significant characteristic features of cancer development and progression, several cancer treatment strategies have been anticipated (Hanahan and Weinberg, 2011). In addition to these major treatment strategies, a number of other strategies, namely; surgery, chemotherapy, immune therapy, radiation therapy, hormone therapy, targeted therapy and palliative care are also worth mentioning. In this direction which treatments are used, depends on the type, location and grade of the cancer as well as the patient's health and preferences (Miller *et al*., 2016; Falzone *et al*., 2018). Moreover, the hyperthermia approach in which increases the temperature of tumor-loaded tissue (40-43°C) as an adjunctive therapy is used with other established cancer treatments such as chemo and radiotherapy (Wust *et al*., 2002).

1.3.2 Drawback of current treatment regime

There are two major challenges for the success treatment of cancer, tumour heterogeneity and emergence of drug resistance. Both the challenges are being closely related leading to the therapeutic failures in clinical practice (Zugazagoitia *et al*., 2016a). Furthermore, in many cases, cancerous cells originate from a single cell with stem cell characteristics. These characteristics have a profound effect on the treatment of cancer as the drugs that are more target-specific can cause the regression of the bulk of the tumor, but in most cases fails to eliminate the cancer stem cells and results in recurrence of the tumor after the discontinuation of the drug administration (Chakraborty and Rahman, 2012). Furthermore, surgery, radiation and chemotherapy, the three main approaches to cancer treatment have several drawbacks. On one hand, damage of healthy tissues and cells occurs in surgery and radiation, conversely the fatigue from radiotherapy which may last for the duration of the treatment or months afterwards occurs. Similarly, untargeted radiotherapy suffers from a lack of specificity. Chemotherapy is the only approach which is systemic, meaning that the drugs circulate through the bloodstream reaching cancer cells in all body tissues. It can annihilate both original tumor cells as well as metastasized ones. The drawback of this approach is that the existing chemotherapeutic drugs are toxic to all cells including cancer as well as to normal cells. So, the administrations of these toxic agents kill the rapidly proliferating cancer cells along with the normal cells which may lead to several severe side effects that affect the patient's lifestyle and also resistance may be developed by cancer cells (Chakraborty and Rahman, 2012).

2. Phytochemicals as multitarget anticancerous molecules

Phytochemicals, *i.e.*, plant derived natural products (NPs) have gained importance as therapeutic molecules because they possess wide range of pharmacophores and, thus a high degree of stereochemistry (three-dimensional, spatial arrangement of atoms within molecule) facilitating target binding (Harvey *et al*., 2015; Warrier, 2021). More than 85 thousand plant species have been referenced globally for their medicinal uses (Lahlou and Lahlou, 2013). NPs are relatively safer with little or no side effects and generally, have a lower cost, thereby holding immense promise for the discovery and development of new pharmaceuticals in diverse human diseases including cancer (Ngo *et al*., 2013; Singh *et al*., 2018; Khan and Ahmad, 2021; Husain, 2021). Moreover, most of the Food and Drug Administration approved drugs are either natural products or derivatives of natural products (Newman and Cragg, 2012). Overall, natural product research is a vigorous tool to discover novel biologically active components with unique mode of action.

Exploring NP databases may give valuable and novel anticancer drugs (Ngo *et al*., 2013; Palomino *et al*., 2009). At present, the largest freely available resource for NPs is the Universal Natural Products Database (UNPD) which holds a total of 197201 NPs of plants, animals and microbial origin. The various other NP databases and chemical libraries such as NuBBE (Valli *et al*., 2013), CamMedNP (Ntie-Kang *et al*., 2013a), Super Natural (Dunkel *et al*., 2006), HIT (Ye *et al*., 2011), NPACT (Mangal *et al*., 2013), TCM Database @ Taiwan (Chen, 2011), TCMID (Xue *et al*., 2013), HIM-herbal ingredients *in vivo* metabolism database (Kang *et al*., 2013) and AfroDB (Ntie-Kang *et al*., 2013b) are also available for public use without any restraints.

In view of the fact that phytochemicals show higher diversity as compared to synthetic compounds because chemical space covered by synthetic compounds is limited; it is sensible to indicate that chemical leads can be produced that are able to interact with multiple therapeutic targets (Lahlou and Lahlou, 2013; Pratap *et al*., 2021; Yeligar *et al*., 2021) Thus, in the following section, an array of phytochemicals are presented which are capable of interaction with multiple therapeutic targets.

2.1 Rutin

Rutin is a flavonoid found in a wide variety of plants and used as nutraceutical agent. It is nontoxic and naturally present in various food products of plant origin especially buckwheat seeds, apricots,

tea, cherries, grapes, grapefruit, onion, plums, and oranges (Prasad and Prasad, 2019). Various *in vitro* and *in vivo* studies have well established the anticancer, chemopreventive and chemosensitizing role of rutin against numerous cancers (Lin *et al*., 2012; Chen *et al*., 2013; Calzada *et al*., 2018). Thus, *in vitro* study of Chen and his team demonstrated anti-neuroblastoma effect of rutin, where, rutin significantly inhibited the growth of LAN-5 cells and chemotactic ability (Chen *et al*., 2013). The study demonstrated that rutin decreased BCL2 expression, BCL2/BAX ratio, reduction in MYCN mRNA level and the secretion of TNF-α in LAN-5 cell line. Study of Calzada and his team also reported the anticancer activity of rutin against human leukemic monocyte lymphoma U-937 cell line (Calzada *et al*., 2018). Rutin has been reported as anticancer agent against colorectal carcinoma in human by cell cycle arrest and/or apoptosis machanism in CRC cell line (Araújo *et al*., 2011). Rutin also reported to reduce benzo(a)pyrenediol epoxide induced cyclooxygenase-2 (COX-2) expression by suppressing the Raf-MEK-ERK and protein kinase-B (AKT) signaling pathways (Choi *et al*., 2014). Rutin was also found to down regulate the levels of inflammatory markers like tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and expressions of p38-mitogen-activated protein kinase (p38-MAPK), nuclear factor-8B (NF-κB), inducible nitric oxide synthase (iNOS) and COX-2 (Nafees *et al*., 2015) that made it an efficient anticancer agent.

Additionally, various *in vivo* studies also confirmed the anticancerous role of rutin. Thus, the study of Alonso-Castro and his team reported that rutin significantly reduced tumor growth in mice xenografted with SW480 colon cancer cells. This study demonstrated that rutin drastically reduced the nuclear accumulation of NF-κB and activated protein-1 (Alonso-Castro *et al*., 2013). Extract of *Prunella vulgaris* enriched in rutin showed inhibition of tumor growth in C57BL/6 mice. Tumor reducing effect of rutin has also been reported in mice intraperitoneally injected with WEHI-3 cells; it reduced the size of enlarged spleen in mice (Lin *et al*., 2012). Rutin also avert inflammatory responses in UVB-irradiated mouse skin mechanistically by inhibiting the phosporylation level of signal transducer and activator of transcription-3 (STAT-3) (Choi *et al*., 2014). In another *in vivo* study, rutin was found to inhibit spleen leukemia tumor growth in a WEHI-3 leukemia murine model. Study also revealed that rutin promote immune response associated with an increase in the activity of macrophage phagocytosis (Lin *et al*., 2012). The anticancer effect of rutin-cisplatin amalgamation against malignant murine ascites dalton's lymphoma (DL) confirmed with increased cytotoxicity and apoptosis in DL cells resulting in increase in host's survival (Prasad and Prasad, 2019). Other study demonstrated that human leukemia HL-60 cells were implanted into mice and treated with vehicle rutin resulted in a reduction of tumor weight and volume (Lin *et al*., 2012). Study of Elsayed and his team suggested that C-met kinase as a potential mechanistic target for rutin-mediated anticancer effects on triple negative breast cancer (TNBC) cell lines also reduce the TNBC in nude mouse mode (Elsayed *et al*., 2017). These studies therefore, clearly showed the functional dietary flavonoid rutin as a potential agent for prevention and control of different cancer by hitting multiple targets.

2.2 Curcumin

Curcumin, a natural polyphenolic compound, present in the rhizomes of turmeric (*Curcuma longa*). Particularly, the anticancer effects of curcumin have been widely deliberated in various *in vitro* and *in vivo* studies (Awasthi *et al*., 2017; Singh *et al*., 2018). Curcumin was found to interfering with multiple targets and signalling pathways involved in cancer cell proliferation, invasion and metastasis (Wang *et al*., 2019). Kunnumakkara and his team described that curcumin play a very crucial role in cancer prevention through interference with multiple targets and signalling cascades including phosphoinositide 3-kinase (PI3K)/AKT pathway, Wnt/β-catenin signaling, MAPK pathway, Janus kinase (JAK)/ STAT signaling pathway, NF-8B pathway and p53 signaling (Kunnumakkara *et al*., 2017). Curcumin has also been reported to intend oncogenic and tumor suppressive miRNAs in a study of Momtazi and team (Momtazi *et al*., 2016). Curcumin was also found to inhibit STAT-3 and NF-κB signaling pathways as well as the inhibition of COX-2 and 5-LOX responsible for cancer development and progression. Another study showed the inhibitory effect of curcumin on immortalized oral mucosal epithelial cells and squamous carcinoma cells (SCC4) (Chakravarti *et al*., 2010). Furthermore, curcumin also has been reported to induce cell death in many animal and human cell lines, including melanoma, leukemia, breast, kindney, lung, colon, liver and ovaries (Karunagaran *et al*., 2005). *In vivo* studies performed by Dorai and his team showed that curcumin has a strong ability to reduce proliferation and induce apoptosis in prostate cancer by interfering MAPK, epidermal growth factor receptor (EGFR) and NF-κB pathways (Dorai *et al*., 2001). Inhibitory effect of curcumin along with radiation therapy was also reported against colorectal carcinoma due to its ability to target NF-κB. Curcumin has also been reported to possess *in vivo* growth suppressive effects on head and neck squamous cell carcinoma using nude mouse xenograft models (Chakravarti *et al*., 2006). Thus, curcumin showed wide range of anticancer effect against different types of cancer *via* multiple mechanisms such as interfering with different cellular pathways and inducing/inhibiting the fabrication of various types of growth factors and cytokines (Tomeh *et al*., 2019).

2.3 Quercetin

Quercetin is a naturally occurring polyphenolic flavonoid, commonly found in different fruits and vegetables such as capers, lovage, dill, cilantro, onions, apples, and berries (Anand David *et al*., 2016). Quercetin has been reported to inhibit propagation of various types of cancers such as liver, lung, colon breast, prostate and cervical cancer (Iacopetta *et al*., 2017; Liu *et al*., 2017). Quercetin was reported to alter multiple targets, cellular signaling and the ability to inhibit enzymes responsible for the activation of tumorigenesis. In addition, quercetin has been recently reported to have significant synergistic effects with chemotherapeutic agents such as cisplatin (Brito *et al*., 2015). In a study, it has been reported that quercetin enhanced apoptosis and mRNA expression levels in breast cancer cells (MCF-7). Quercetin was also found to reduce cellular NAD(P)H quinone oxidoreductase and multidrug resistant protein gene expression level (Minaei *et al*., 2016; Suksiriworapong *et al*., 2016). Similarly, quercetin buried the expression of cyclin-D1, twist, p21, and phospho p38-MAPKs in MCF-7 and MDA-MB-231 breast cancer cell lines (Liao *et al*., 2015; Ranganathan *et al*., 2015). Li and his team reported the inhibitory effect of quercetin on colon cancer cells CT26 and MC38. This study suggested that quercetin induced apoptosis through the MAPK pathway and regulate the expression of epithelial-mesenchymal transition (EMT) markers. Another study on colon cancer demonstrated that quercetin target colon cancer stem cells (CSCs) and significantly inhibit to the Notch-1 signaling (Li *et al*.,

2020). In has been also reported that quercetin regulate the expression of EMT markers and decrease the production of different inflammation factors (TNF-α, IL-6, and COX-2) as well as metastasis-related proteins in colon cancer cells (Song *et al*., 2016). Quercetin also suppressed the proliferation of pancreatic cancer cell by reducing the expression levels of cellular FLICE-like inhibitory protein and inhibition of EGFR-mediated FAK, AKT, MEK1/2, and ERK1/2 signaling pathway (Lee *et al*., 2015; Kim *et al*., 2016). Study of Park and his team reported that quercetin inhibit cell proliferation and induced cell cycle arrest in vaginal cell (VK2/E6E7) and endo cervical cell (End1/E6E7) cells through the down-regulation of ERK1/2, P38-MAPK and AKT signaling molecules (Park *et al*., 2019). Zhao reported that quercetin inhibit cell proliferation and migration by regulating miR-16 and HOXA10 axis in oral cancer (Zhao *et al*., 2019)

Furthermore, various *in vivo* studies have looked at the anticancer effect of quercetin in various xenograft models. The life span of tumor-bearing animal models was significantly increased and the tumor growth and volume was reduced after treated with quercetin. The inhibitory effect of quercetin reflected in the promotion of apoptosis, inhibition of proliferation, angiogenesis and metastasis (Tang *et al*., 2020). It has been reported that different doses of quercetin promote apoptosis and cell cycle by inhibiting Akt/mTOR pathway in breast cancer and leukemia cell xenograft models (Maso *et al*., 2014; Rivera *et al*., 2016). Yang and his co-workers reported that quercetin reduced tumor growth in prostate cancer model mice by up-regulating the expression of thrombospondin-1 (TSP-1) (Yang *et al*., 2016). Quercetin was also found to inhibit angiogenesis in BALB/c mice model of breast cancer by inhibiting the calcineurin/NFAT pathway. Study of Kee and his team has demonstrated the inhibitory role of quercetin on colorectal lung metastasis (Kee *et al*., 2016). The inhibitory effect of quercetin on allogeneic tumor growth was also found in tumor cell models such as lung cancer, pancreatic cancer (Wang *et al*., 2014). These studies suggested quercetin adequately considered as a therapeutic multitarget agent against various cancers.

2.4 Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is a component (catechin) extracted from green tea. EGCG has many therapeutic effects against pathological conditions including cancer (Chu *et al*., 2017). Various *in vitro* and *in vivo* studies have demonstrated that EGCG prevents tumor proliferation by acting against angiogenesis (Jung *et al*., 2001). EGCG showed anticancer effects against numerous types of cancer including lung, oral-digestive tract, breast, colorectal, prostate cancer, melanoma, acute myelogenousleukaemia, multiple myeloma and chronic myelogenous leukaemia without affecting normal cells (Kim *et al*., 2014; Tsukamoto *et al*., 2014; Huang *et al*., 2015). EGCG impede various signalling pathways and biological mechanisms related to cancer growth and progression. Shankar and his team members reported that EGCG inhibit PI3K/AKT and ERK pathways and activation of FKHRL1/FOXO3a in pancreatic cancer (Shankar *et al*., 2013). EGCG was also reported to interfere with several targets of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt, and Notch signalling pathways (Granja *et al*., 2016). Some *in vitro* studies illustrated that EGCG suppressed angiogenesis in lung and breast cancer cells by inhibiting VEGF expression through repression Hypoxia-inducible factor 1-α (HIF-1α) and NF-κB (Wang *et al*., 2011). EGCG can also inhibit the expression of the anti-apoptotic proteins BCL-2 and BCL-XL and induce the expression of apoptotic proteins BAX and BAK, with subsequent activation of caspases in numerous types of cancers (Sonoda *et al*., 2014). Moreover different *in vitro* studies showed that EGCG significantly inhibit the activation and nuclear translocation of NF-kB transcription factor to impede the cancer progression in different cancer cells (Qin *et al*., 2012).

Furthermore, various *in vivo* studies proved the anticancer effect of EGCG in different cancer model. Hwang and his team reported that EGCG inhibit cancer invasion via repressing functional invadopodia formation and FAK/Srcsignalling in male BALB/c athymic nude mice (Hwang *et al*., 2013). EGCG also reported to inhibit VEGF expression *via* suppressing STAT-3 activity into BALB/c nude female mice against adenocarcinoma (Zhu *et al*., 2011). In another study, EGCG was found to inhibit HGF-induced cell growth and invasion through increasing apoptosis in xenograft tumor growth model (Koh *et al*., 2011). EGCG reduced tumor growth in esophageal cancer model *via* suppressing the expression of Ki67, p-ERK1/2 and COX-2 (Ye *et al*., 2012). Another *in vivo* study suggested that EGCG reduced tumor weight in breast cancer by inhibiting the expression of the VEGF (Wei *et al*., 2018). Thus, these *in vitro* and *in vivo* studies confirmed that EGCG has multitargated effect against various types of cancer.

2.5 Resveratrol

Resveratrol is a naturally occurring polyphenol found in lots of dietary substances, such as grapes, nuts, wine, flowers, legumes, berries and many other human foods (Berman *et al*., 2017). In various *in vitro* studies, it has been reported that resveratrol showed cytotoxic effects against a large range of human tumor cells, including myeloid cancer, lymphoid cancer, breast, skin, cervix, ovary, stomach, prostate, colon, liver, pancreas, and thyroid carcinoma cells (Harikumar *et al*., 2010; Tomé-Carneiro *et al*., 2013). Ji and his team reported that resveratrol showed anticancer effect against LoVo cells by suppressing the TGF-β-induced EMT markers. Resveratrol was also found to inhibit the invasive and migratory ability of LoVo cells, increase in the expression of E-cadherin and inhibition of the TGF-β1/Smads signaling pathway (Ji *et al*., 2015). Resveratrol showed anticancer effect against colon cancer cell lines, mainly in relation to the DNA-damage response (DDR; PIKKs-Chks-p53 signaling cascade) and its cellular consequences (Colin *et al*., 2014). Moreover, Resveratrol exhibited antigrowth activity against 3D cell aggregates of the SKOV-3 and OVCAR-8 ovarian cancer cell lines by reducing the phosphorylation of Her-2 and EGFR. Study also showed the significant decrease in the expression of extracellular-signal-regulated kinases and vascular endothelial growth factor (Hogg *et al*., 2015). Similarly, another study showed that resveratrol inhibits cisplatin-induced epithelial-to-mesenchymal transition, a key process in cancer progression in ovarian cancer cells (Baribeau *et al*., 2014). Anticancer effect of resveratrol has been known against cervical cancer by raising the apoptosis in cells by inhibiting STAT-3, Notch pathway, and Wnt mediated signaling pathways. Resveratrol found to suppressed cell proliferation in oral squamous cell carcinoma cell lines by increasing apoptosis and expression of cyclin A2 and cyclin B1 (Yu *et al*., 2015).

Furthermore, many *in vivo* studies showed the anticancer effect of resveratrol against various cancers. The effect of resveratrol has been reported on phosphatase and tensin homolog (PTEN)/AKT pathway in mouse model of melanoma. Resveratrol was found to reduce tumor volume and metastasis through reduced protein kinases

expression (Bhattacharya *et al*., 2011). In addition, resveratrol was found to inhibit tumor production in a genetically engineered mouse model of sporadic CRC by epigenetically down regulating Kras by raising the expression of miR-96 (Saud *et al*., 2014). Resveratrol is well known to reduce the onset of skin cancer induced by 12-dimethylbenz[a]anthracene (DMBA) in CD-1 mice (Soleas *et al*., 2002). Moreover, resveratrol was also reported to protect hairless SKH-1 mouse against UVB mediated skin cancer (Reagan-Shaw *et al*., 2004). In addition, resveratrol has been reported to decrease COX-2 enzyme by maintaining adequate zinc levels in benzo[a] pyrene-induced lung carcinogenesis in mice (Malhotra *et al*., 2011). Concisely, resveratrol has been found to interfere with various cancers by targeting several molecules and pathways involved in cancer development.

2.6 Tocotrienol

Tocotrienols (TTs) are found in naturally occurring sources such as red palm oil, some vegetables oil, wheat germ, barley, annatto seeds, rice bran and certain types of seeds. Various *in vitro* and *in vivo* studies reported the therapeutic role of TTs against many chronic diseases especially its significant antitumor effect against cancers (Rizvi *et al*., 2014). TTs have been reported antiproliferative/ proapoptotic effects to reduce the metastatic or angiogenic properties in different cancer cells (Kanchi *et al*., 2017; Montagnani Marelli *et al*., 2019). Several studies were reported significant anticancer effect of TTs against different tumors such as skin, lung, prostate, breast cancer and colon cancer (Chin *et al*., 2016; Peh *et al*., 2016). Constantinou and his team reported anti cancer activity of TTs against estrogendependent (MCF-7) and estrogen-independent (MDA-MB-231) breast cancer cells by promoting G1/S cell-cycle inhibition (Constantinou *et al*., 2020). In prostate cancer cells, TT has been found to suppress the expression of an angiogenic promoter named Ang-1 at transcription and translation level (Tang *et al*., 2019). Parajuli and team demonstrated antiproliferative effect of γ-tocotrienol against human breast cancer cells mediated by the inhibition of Akt/mTOR signaling, c-Myc expression and aerobic glycolysis (Parajuli *et al*., 2015). Similarly, TT has also been reported as antiproliferative against breast carcinoma cells by inducing apoptosis in tumor cells through endoplasmic reticulum stress (Park *et al*., 2010) and apoptosis through activation of caspases and inhibition of tumor cell growth by suppressing 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGR activity) (Wali *et al*., 2009). Moreover, TT also found to inhibit proliferation in human cervical cancer HeLa cells by up-regulating IL-6 and down-regulating cyclin D3, p16, and CDK6 expression (Wu and Ng, 2010),

Numerous anticancer effects of TTs have also been demonstrated in various preclinical models. Kunnumakkara and his team reported that TT reduced the expression of Ki-67, COX-2, MMP-9, NF-κB, p65 and VEGF in orthotopic nude mouse model of human pancreatic cancer (Kunnumakkara *et al*., 2010). Another study demonstrated that TT reduced the activation of AKT, NF-κB and also mitigates the levels of COX-2, cyclin D1, CDK2, CDK4, and CDK6 in mammary syngeneic model for breast cancer (Ananthula *et al*., 2014). Study of Prasad and his team demonstrated that TT was found to reduce the tumor growth in xenograft colorectal cancer model *via* diminish Ki-67, cyclin D1, MMP-9, CXCR4, NF-κB/p65, and VEGF pathways. It has been also reported that TT inhibit vessel formation, tumor growth and angiogenesis in orthotopic liver cancer mouse model by suppressing the activation of AKT/mTOR pathway (Prasad *et al*., 2016). Luk and his team illustrated in their study that oral administration of γ-tocotrienolwas found to suppress tumor formation in >70% of mice subcutaneously injected with prostate cancer cells (Luk *et al*., 2011). Thus, these *in vitro/in vivo* experiments clearly demonstrated the potential anticancer properties of TTs against different cancers by affecting many targets, enzymes and signaling pathways.

2.7 Kaempferol

Kaempferol is a natural dietary flavonoid mostly found in apple, apple, tomato, green tea, pine, *Angelica decursiva*, beans, broccoli, cabbage and ginkgo leaf. Intake of kaempferol is associated with low occurrence of different types of cancer, such as skin, liver, colon, ovary, pancreas, stomach, and bladder cancer (Pei *et al*., 2017). In addition, it has also been reported that kaempferol inhibited different types of cancer cells by triggering cell cycle arrest at G2/M phase, apoptosis, down regulation of various signaling pathways such as PI3K/AKT, expression of matrix metallopeptidase 2 (MMP-2), metastasis-related markers and EMT markers (Imran *et al*., 2019). Kaempferol has been reported to inhibit the growth of breast cancer cell lines at micromolar concentrations (Lee *et al*., 2018; Zhu and Xue, 2019). These study suggested that kaempherol increased the levels of pro-apoptotic enzymes and proteins, such as cleaved caspase 3, 7 and 9, p21, p53, Bax, PARP, and p-ATM and attenuate the levels of Bcl2, polo-like kinase 1 (PLK-1), pAKT, phosphorylated insulin receptor substrate 1 (pIRS-1), phosphorylated mitogen-activated protein kinase (pMEK)1/2, cyclin-dependent kinase 1 (CDK1), cyclins A, B, D1, and E, and cathepsin D (Tsiklauri *et al*., 2011; Diantini *et al*., 2012).

Study of Zhu and his team revealed that kaempferol significantly inhibit human hepatic cancer cells proliferation (HepG2, SK-HEP-1, Huh7) in a dose-dependent manner (Zhu *et al*., 2018). Kaempferol was also found to prevent cell migration and invasion by inducing cell apoptosis and cell cycle arrest at the G2/M phase (Zhu *et al*., 2018). In a number of studies, the antiproliferative effect of kaempferol against liver cancer cells by decreasing the expression level of miR-21, cytokine signaling-3, signal transducer and activation of CDK1, cyclin B, STAT-3, PI3K/AKT/mTOR and p-mTOR signaling pathway have been reported (Wonganan *et al*., 2017; Lee *et al*., 2014). Kaempferol was also reported to possess cytotoxic effects on different human colorectal cancer cells lines, including HCT116, HT-29, HCT-15, LS174-R colon and SW480 cells by modulating the expression of MAPK, JAK/STAT3, PI3K/AKT, ATM, H2A histone family member X (H2AX), phospho-p38, p21, p53, Bcl-2 and NF-κB (Riahi-Chebbi *et al*., 2019). Kashafi and her team reported that kaempferol selectively inhibit the growth of human cervical cancers cells via cell cycle arrest, apoptosis associated with downregulation of PI3K/AKT and human telomerase reverse transcriptase (hTERT) pathways (Kashafi *et al*., 2017). Kaempferol was also reported to inhibit proliferation of prostate cancer cell lines (LNCaP) by downregulation of androgen receptor expression and upregulation of caspase 3, 8, 9 and poly (ADP-ribose) polymerase proteins (Halimah *et al*., 2015).

Furthermore, numerous *in vivo* studies have also suggested that kaempferol reduced tumor growth by interfering various targets and pathways. Another study showed that kaempferol significantly enhanced the rate of survival as well as reduced the growth of prostate cancer in athymic nude mice (Mamouni *et al*., 2018). Kaempferol

encouraged the degranulation in basophilic leukemia (RBL-2H3) cells by reducing the release of beta-hexosaminidase in a rat model of leukemia (Xu *et al*., 2009). Kaempferol was also found to inhibit the volume of subcutaneous xenograft in lung metastasis model (Qin *et al*., 2016). It also has been reported that kaempferol suppressed tumor growth as well as cancer growth and invasion in BALB/c(nu/nu) mice inoculated with human osteosarcoma cell by upregulation of apoptosis markers and downregulation of growth associated markers (Dang *et al*., 2015). Kim *et al*. (2016) reported that kaempferol reduced breast cancer cells growthinxenografted mouse model via nongenomic ER signaling pathway associated with IGF-1R. Thus, these *in vitro* and *in vivo* studies clearly demonstrated the potential anticancer properties of kaempferol against various cancers by affecting multiple targets, enzymes and signaling pathways.

3. Conclusion

Development of cancer treatment, prevention and general health care products from phytochemicals have a broader prospect, greater economic and social benefits when compared with prevalent synthetic anti-cancerous drugs. Considering the fact that efficacy and safety of herbal products further research can improve appropriate use of plant products drastically. In cancer cells, many signaling pathways operate in parallel, drug combinations against several molecular alterations or cancer, might be a promising therapeutic strategy to treat cancer. Phytochemicals have been the source of the active therapeutic agents and play unique role in the identification of new drugs and new drug-lead compounds with high selectivity and low toxicity. In this review, emphasizes the therapeutic potentials of multi-target anticancer phytochemicals. This assemblage will help to understand the recent trends and insights in front of the scientific community working in dual or multi-inhibitors and help them in designing the next generation of multi-targeted anticancer agents. In addition by the structure based drug desigining methods, a huge number of plant derived metabolites can be screened for their drugability and pharmacokinetic properties. Inhibitory effect of these metabolites against more than one target of cancer can be easily explored by the molecular docking and molecular dynamic simulation analysis. Furthermore, omics data explosion grant a break through for computational analysis of anticancer drugs and improve the efficiency of drug prediction. High-throughput transcriptome data were widely used in biomarkers' identification and drug prediction by integrating with drug-response data. For the anticancer drug discovery, biological network theories as well as methodology were also applied successfully such as analysis based on drug-traget network, protein-protein interaction network and diseasegene network.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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