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Anti-Cancer Properties of Plant and Plant Derived Secondary Metabolites: A Brief Review



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ABSTRACT

Plants and its secondary components are being used from decades against several diseases, also for cancer, the most common and deadliest diseases in world. The modern science still struggling to cure this disease but several treatments mediated problems are not under control, specifically side effects of chemotherapy. On the other some of the plant and its active compounds are discovered by several scientist that's not only showing anticancer properties but also found with fewer side effects and some of them are less toxic for humans. So in this regards, use of plants and its compounds against cancer is very beneficial and thus need to be upheld it's used and further more research for better treatments. Here in this article we discussed about anticancer plants, the active compounds. Our objective is to point out current challenges in this field and to evaluate their therapeutic usage and future opportunities against Cancer.



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INTRODUCTION:

It is well known to us that 9.6 million people died in 2018 only for cancer [63]. Several practices like, surgery, chemotherapy and radiation therapy have been used in this field but the disease not fully curable still now[2,3,4] that is mainly due to metastases process[5]. Therefore, all over world cancer is now an important topic of research. Use of plants and its components are used since very long period of time because of their therapeutics values [6,7]. The secondary metabolites that are mainly found from the higher plants are flavoring agents, fragrant molecules, phytochemicals like alkaloids, flavonoids, polyphenols, and food additives, are also used against cancer *in vivo* and *in vitro*[8,9]. There are also so many drugs those are isolated previously from plants that can act against cancer [63], and the interesting fact is here that only 15%, approx. 250,000 plants are investigated [9,10]. Different kinds of phytochemical constituents can improve efficiency of chemotherapeutic agents, decreases the resistance of chemotherapeutic drugs, lower and alleviate the adverse side effects of chemotherapy[9]. Another report by WHO(World Health Organization) supports that approx. 80% population from developed countries prefer these plant based medicines and thus used broadly in anticancer agents also being cost-effective and easily to access [63,9]. On the other, we know that these plants and its metabolites also served a key role in drug development process also. After the sequencing of human genome, so many innovative molecular symbols have been acknowledged as significant in several illnesses [63,48]. Some of the known drugs are like, indirubin, which selectively halts cyclin-dependent kinases [49,50]. Exatecan, act as an analog of camptothecin out-of-the-way from *Camptotheca acuminata Decne.* (Nyssaceae) is being reputable as an anticancer moderator [51]. Vinflunine is use as an anticancer agent with heightened efficiency [52,53]. So as the background supports plants and its derived molecules can be used against cancer we must focus this field with more concerns. There are so many studies and research yet to be performed in the future. In this review, we will address the plant derived compounds, its anticancer role in brief, and some of the problems in cancer research.

What are the plants agents that act against cancer?

Epigallocatechin-3-gallate (EGCG), used against cancer. It has the capacity to efficiently reduce the amount of free radicals [9,10,11,12], exert anti-proliferative effects by blocking the activation of transcription factors AP-1 and NF- κ B, function in G0/G1 arrest and it also induces apoptosis in different cancer like breast and stomach cancer [18,44].

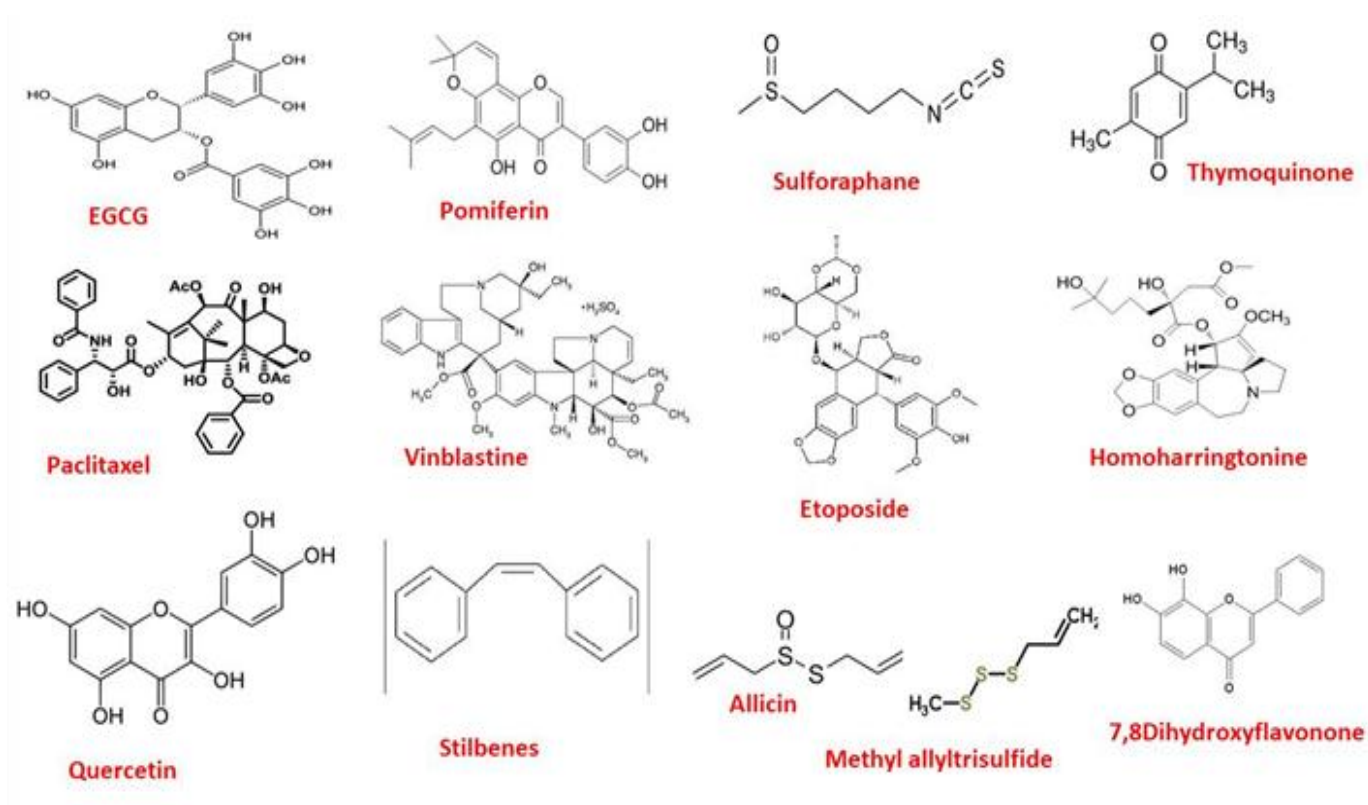


Figure No. 1: Structure of plant derived anticancer component [10, 7, Google search and pubchem].

The Pomiferin, and Sulforaphane, that are also known to inhibits histones deacetylases (HDAC enzyme)[13,14]. Induction of apoptosis and oxidative stress in breast and lung cancer all also special features of this compound [20,10]. Thymoquinone induce apoptosis, helps to arrest cell cycle and inhibit growth of different cancer [15,22,24].

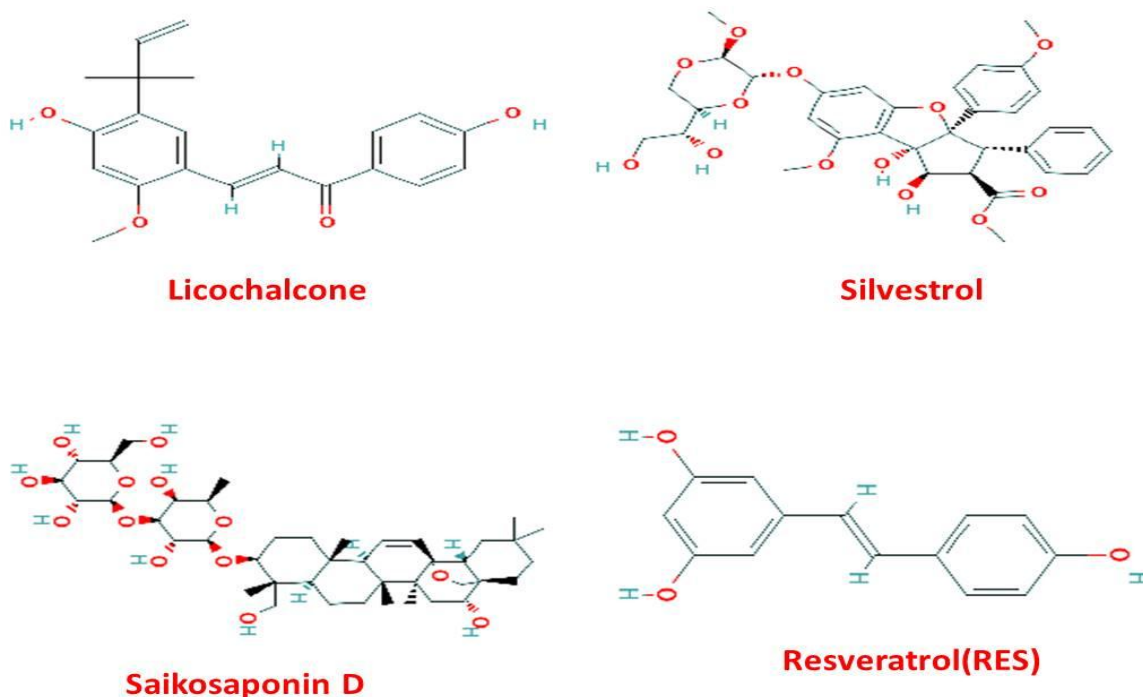


Figure No. 2: Structure of plant derived anticancer component

[<https://pubchem.ncbi.nlm.nih.gov/>].

Paclitaxel, famous for disrupting the microtubules and finally inhibit cell proliferation, induced cell death in carcinoma, breast and lung cancer [16,25,45]. There are other compounds like vinca alkaloids (vinblastine) are involved with M phase arresting [63]. Lignans (etoposide) that stable the topoisomerase II-DNA complex thus finally causing permanent double strand breaks [46,63]. Homoharringtonine regulate translation process [63]. Flavones (Quercetin) prompts apoptosis [17] and down regulates of the appearance of epidermal growth factor receptor (EGFR)[16,63]. Stilbenes (Combretastatin prodrug) has anti-neoplastic properties are involved in mitotic arrest [63]. Last but not the list Resveratrol (RES) also showing a great function against cancer as it has ant proliferative and pro apoptotic effect against cancer [55,57].

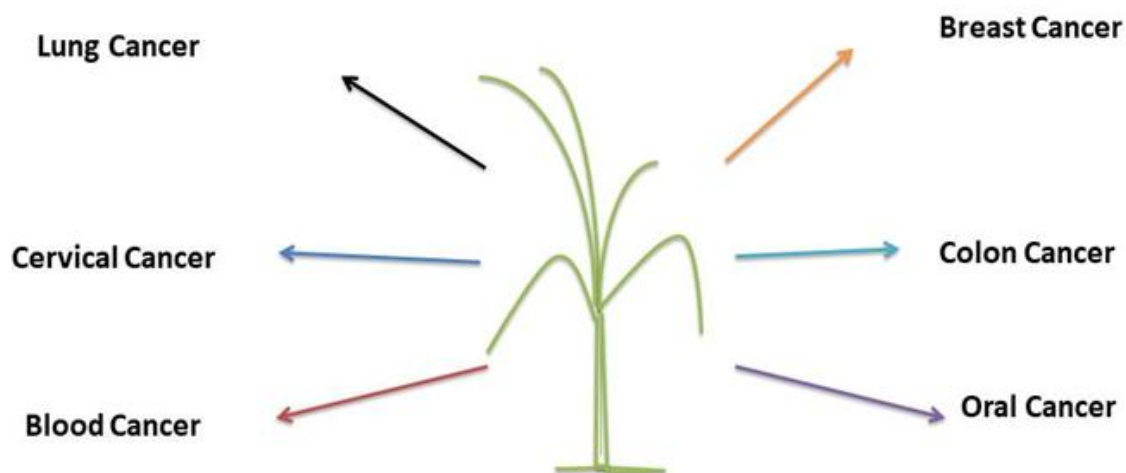


Figure No. 3: Plants impact on Different Cancer types [modified from Khan, T *et al.*, 2020].

All these drugs are plant derived compounds (the structure presented in fig 1 and 2) have anti-cancer events supported by previous researches. Also, there are many medicinal plants which have been examined in different cancer cell lines and they showed positive effect [9]. In the below table 1 we have summarized the function of different compound against different cancer.

Table No. 1: Plants and Plant derived secondary compounds and its anticancer features:

Compound	Source Plant	Mode of Action	Cancer Types	Reference
EGCG(epigallocatechin-3-gallate)	Green tea	Exert anti proliferative effects on transcription factors AP-1 and NF-kB, cell cycle, G0/G1 arrest, and it also induced apoptosis.	Leukemia, stomach, pancreas and breast	17,18,10,42,43,44
Pomiferin	<i>Osage orange</i>	HADC enzyme inhibitor	kidney, lung, prostate, breast	13,10
sulforaphane	Broccoli	Induced oxidative stress, apoptosis and HDAC enzyme inhibition	Prostate, breast cancer	19,20
Thymoquinone	Black seed (<i>Nigella</i>)	Inductions of apoptosis, cell cycle, inhibit growth and also	Prostate, colon cancer, and also	21,22,23

	<i>sativa</i>).	inhibit angiogenesis.	skin cancer	,24
Paclitaxel	Bark of <i>Taxus brevifolia</i>	Inhibit cell replication and also induced cell death	Colonic carcinoma, Breast, lung cancer	15,45,63
Vinblastine	<i>Catharanthus roseus</i>	Cells under arrest in M-phase and cell division get stationary.	Lymphomas, advanced testicular breast and lung cancers	1, 63
Etoposide	<i>Podophyllum species</i>	Become stable the topoisomerase II-DNA complex causing in irreversible double strand break,	Lymphomas, bronchial and testicular cancers.	46,63
Homoharringtonine	<i>Cephalotaxus harringtonia</i>	Stops proteins synthesis	Blood cancer	63
Quercetin	Onions, apples, chokeberries	Induction of apoptosis and down-regulation of the expression of epidermal growth factor receptor (EGFR)	Breast, colon, prostate, ovarian, and lung tumor	25,1 16,63
Combretastatin prodrug (Stilbenes)	<i>Combretum caffrum</i>	Causes mitotic arrest by inhibiting tubulin polymerization.	Lung cancer, cervix carcinoma	63
Allicin, methyl allyl trisulfide	<i>Allium sativum</i>	Prevent growth of cancer, induced apoptosis	Colon cancer	26,27,47
Artemisia capillaries extracts	<i>Artemisia capillary</i>	Anticancer activity in vitro, cell motility activity	Liver cancer, carcinoma	28
7,8Dihydroxyflavonone	<i>Alpinia katsumadai</i>	Repressed the growth of human leukemia HL-60 cells	A-549 and K-562, HL-60	29
Silvestrol	<i>Aglaia silvestris</i>	Exhibits dose dependent cytotoxicity	Lung, Prostate and breast	30
Ethanol extract	<i>Boerhavia diffusa</i>	Inhibit S-phase of cell cycle	Hela cell line	31
Saikosaponin D, a saponin	<i>Buplevium</i>	Apoptosis and blocked cycle progression	A-549	32

extract		in G1 phase		
Polysaccharop eptide	<i>Bambyx arundinacea</i>	It suppressed the expression of vascular endothelial growth factor	Carcinoma	33
C.longa extract	<i>Curcuma longa</i>	Inhibition on the proliferation and cell death	colorectal cancer DLD-1 cells	34
Licochalcone	<i>Glycyrrhizagl abra</i>	Effect on apoptosis and cell cycle progression arresting cells in G2/M	Androgen- independent p53- null PC-3 prostate cancer cells.	35
Seed extract	<i>Psoraleacoryli folia</i>	Antibody dependent cellular cytotoxicity, and the antibody complement-mediated cytotoxicity during tumor development.	BGC-823 cancer	36,47
5, 2", 4"- trihydroxy-6, 7, 5"- trimethoxyflav oney and succinic acid	<i>Sorbaria sorbifolia</i>	Upgraded the immune function and strengthen antitumor effects	Sarcoma	37
Resveratrol (RES)	Grapes (<i>Vitis vinifera</i>), mulberries (<i>Morus sp.</i>), and peanuts (<i>Arachis hypogaea</i>)	Anti-proliferative effects, increased ROS production, down regulation Bcl-2 and anti- inflammatory functions.	Breast, prostate, skin, lung, liver, or colorectal cancer	55,56,57

Selected potential Plants derived compounds: Among all the above discussed products some of them are actively used in cancer (table 1 and figure 3). Here in this section, we have discussed some of the plant derived compounds mode of action in cancer cell.

1. Action of Quercetin: In humans, mutations of p53 are the most common genetic deviations that lead to cancer [58]. Quercetin induces p53 stimulation resulting in up regulation of Bax and down regulation of Bcl-2 in tumor cells. This leads to caspase activation and in the end apoptotic cell [59]. A study proved that 248 µM of this molecule

lessening and down regulated p53 protein in human breast cancer cell lines [60]. Its mode of actions are presented in the below diagram Fig.4.

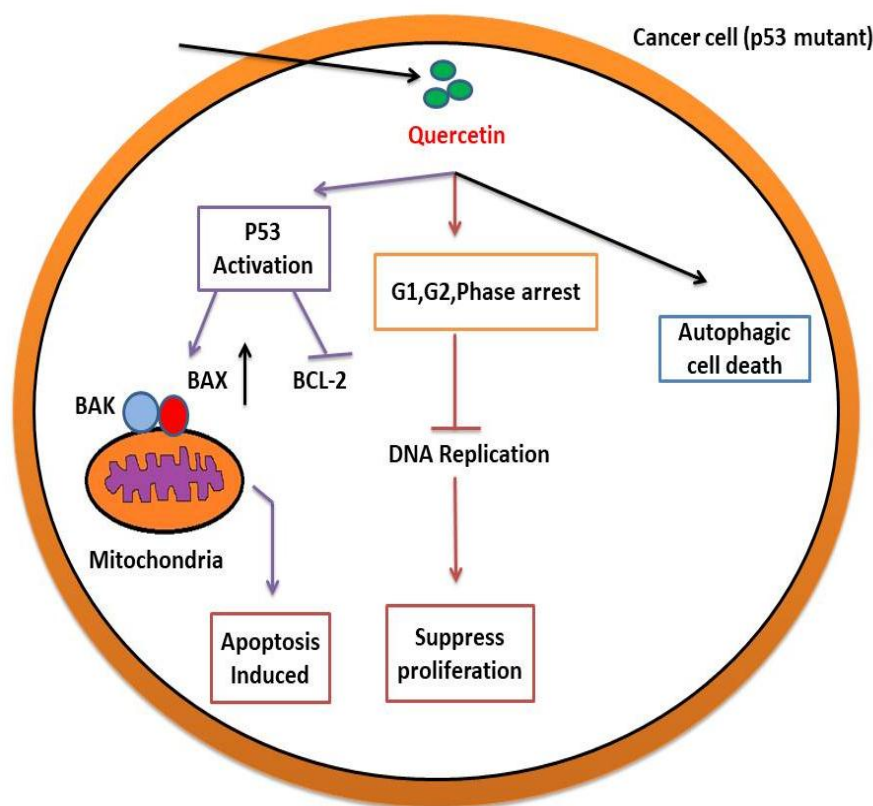


Figure No. 4: Schematics represents brief action of Quercetin in p⁵³ mutant cancer cell.

In 70 μ M deliberation of quercetin, in human, leukemic T-cells were blocked at the late G1 phase whereas G1 phase of cell cycle were halted in gastric cancer, thus reduction in DNA replication [7]. 8-C-(E-phenylethenyl) quercetin, an innovative quercetin derivative, activates G2 phase halt in colon cancer and subdues proliferation, and also encourages autophagic cell death through ERK stimulation[7].

2. Action of Resveratrol (RES): In grouping with other anticancer mediators, RES additively boosts their usefulness counter to countless cancer [57]. It is used with TMZ as it increases the efficiency by dropping ROS/ERK-mediated autophagy and successively maintains apoptosis also both in vitro and in vivo [57]. RES finely tuned the sensitivity to TMZ via activating of the DNA double strands pATR/ pATM/p53 pathway that is principal to the opening of cell death. Furthermore, the variation of GIC connecting p-STAT3(STAT3) it is accountable for tumor existence, angiogenesis, resistance to cell death, and cell cycle

progression) inactivation is well-ordered by RES. [57,61]. This all about how it acts against cancer see Fig.5.

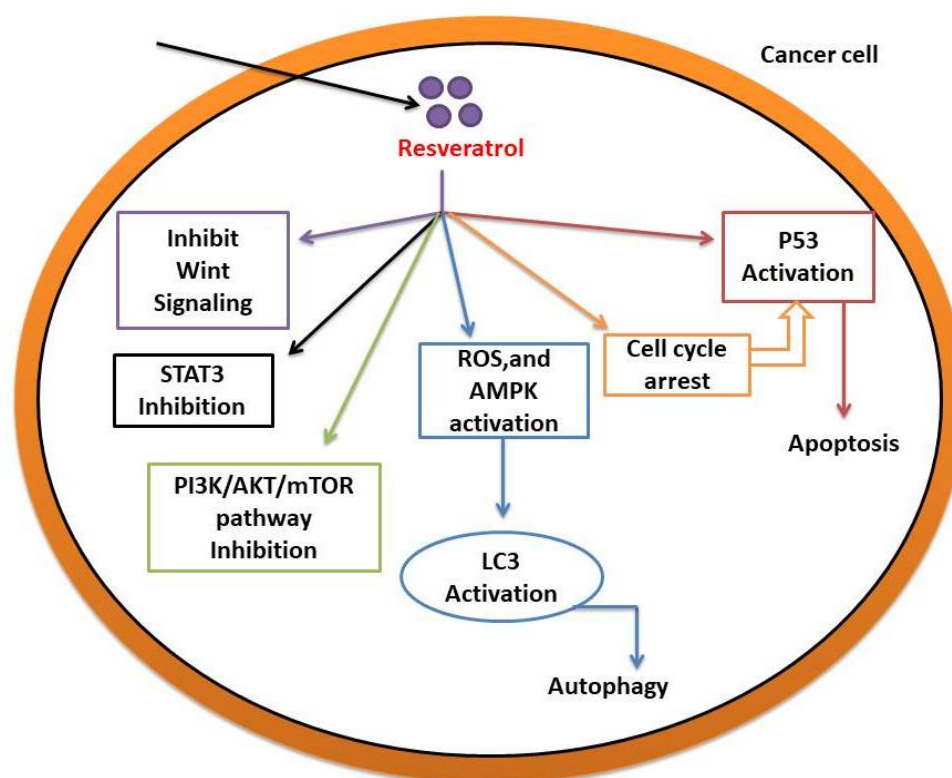


Figure No. 5: Schematics represents action of Resveratrol in cancer cell [modified from Kiskova *et al.*, 2020]

3. Action of EGCG: EGCG major compound of green tea [9]. It reduces the amount of free radicals [10,11,12]. Among smokers, green tea consumption decreased oxidative DNA damage [62]. It is also found that it induced apoptosis in several cancer cell lines, also bar cancer growth, and Neo-angiogenesis [9]. This is the main mode of action of this compound that is also presented as a schematic in Fig.6.

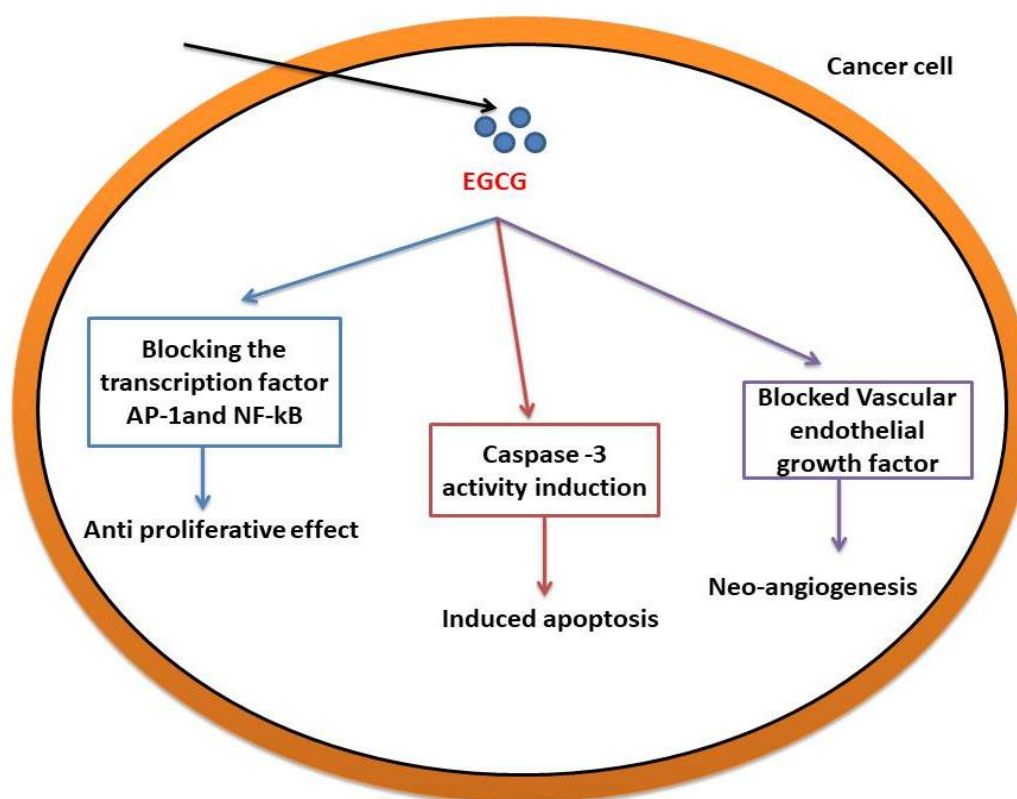


Figure No. 6: Schematics represents action of EGCG in Cancer.

4. Thymoquinone (TQ) mode of action:

TQ cheap drug poisonousness and initiated developments in the drug's anticancer action [9]. The TQ acts as an anticancer agent by stimulating G0/G1 termination in colon, mouse papilloma as well as in canine osteosarcoma cells [9], furthermore G1/S phase arrest in prostate [1], and also G2/M arrest in skin cancer [64]. TQ-induced growth halt is linked to the amplified levels of the cyclin-dependent kinase (CDK) inhibitors p16INK4, p21WAF1, and p27Kip1 [1,23,64] down regulation of androgen receptor, transcription factor E2F-1, and its positive regulator p-Rb [23,9]. It also encouraged apoptosis by up regulation of P⁵³ gene and Caspase -3, and Bax complex bustle and down regulation of anti-apoptotic factor[9]. This sign proves that it is a well-known plant derived compound that can proficiently act against cancer. As you can see that plants and its secondary product has potential role in cancer its ir war rented to explore it more. Use of herbal medicines deals a manner to improve the emergency in drug improvement [38]. The old-style herbal product facts may give rise to a low-priced and faster discovery of new drugs [40], the herbal remedies offer a holistic approach that complements the disease targeted approach [39] and most importantly previous research proved that it is less toxic and also has lower side effect. The central drawback

associated to herbal medicines is the deficiency of international standardization in positions of methods for evaluating their composition, safety, quality and efficacy consistent manufacturing practices, regulation and approval processes [39]. Conversely, some herbal medicines are only allowable by health experts for human uses in the last centuries [40].

Currents problems:

- The mode of action in cancer of all plants and plant derived metabolites still not known.
- Human clinical trials are lacking for some of anticancer plants based products like – RES for brain cancer.
- No data on plants efficiency against cancer in different extraction method.
- Proper documentation of safety is lacking for plants derived molecules.
- How in future the suggested plants can be used successfully as a therapy against cancer?
- Lacking of investigation and research on plants for bio-active compounds.

CONCLUSION

So in this regards, use of plants and its compounds against cancer can be helpful in cancer research and need to be upheld for better treatments. The death occurs for this disease is increasing day by day but there is a huge requirement for a new strategy like use of plants and their secondary metabolites against cancer. Now in the present situation, it is very important for us to prepare for drug development from plants against cancer. We think this work can open a new way towards cancer therapy by using plants. The problems should be resolved in future. that only 15%, approx. 250,000 plants are investigated according to SINGH *et al.*, 2019, thus further laboratory experiments with rest of the unknown plants for new research findings is warranted for cancer treatments in the near future.

Declaration:

All the information presented here after giving appropriate credits to the original authors. The structure of plants derived compounds are taken from direct Google search, <https://pubchem.ncbi.nlm.nih.gov/> and from previously published articles as referenced. We apologies if we missed to cite others valuable papers related in this field due to place issue.

Author's contribution: PC prepared the manuscript under supervision of AD.

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