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Sourav Sikdar and Santanu Debnath

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# Cancer and Alternative Remedies in the Modern Era: A Review

Sourav Sikdar<sup>1</sup> and Santanu Debnath\*<sup>2</sup>

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## ABSTRACT

Cancer is the major health problem in the modern era. According to recent survey, 63% of deaths due to cancer are reported in developing countries. Cancer derives from differential factors like environmental fluctuations, smoking, alcoholism, solar-UV radiation, etc. According to American Institute for Cancer Research, 2018, there are five most common cancers including lung, breast, colorectum, prostate, and stomach cancers, comprising nearly 48.8% of total 34 types of cancers. Surgical resection is the common treatment for cancer patients at earlier stages, whereas patients with later stages are treated with combination therapies, have considerable side-effects on normal cells. Recently, many researchers are targeting on development of biotechnological drugs and anti-tumour vaccines, that have shown promising outcomes in preclinical studies. Advanced cancer cases are often treated with cisplatin or in combination with gemcitabine, docetaxel, etc. that hampers the normal cells too. Therefore, there is a vital demand to develop an agent which has target-specific anti-cancer efficacy without affecting normal cells. Application of natural medicines is extensively made to treat different human diseases whereas cancer is difficult to cure by any agents till today. Traditional medicines including homeopathy, Ayurveda, Unani, etc. are included in the list of alternative remedies often used against cancer.

**Key words:** Cancer, Tumour, Alternative medicines, Herbal extracts, Traditional medicines

Cancer is now a burning issue and is often referred to as the “Pathology of the Century” as it considered as an endemic disease throughout the world [1-2]. According to the survey of National Cancer Institute cancer affects people of different ages. American Institute for Cancer Research, 2018 proposed that there are five major cancers types known as “big-killers” are of lung (12.3%), breast (12.3%), colorectum (10.6%), prostate (7.5%), and stomach (6.1%), comprising 48.8% of total 34 cancers types reported [3]. Cancer is originated by both external factors like tobacco, toxic chemicals, infectious organisms, and radiation and internal factors like hormones, inherited mutations, immune conditions, etc. [4] (Fig 1).

In fact, industrial wastes and agricultural practices of using various insecticides and toxicants, and also the use of various electronic gadgets in daily life have contributed greatly to the enhanced figure of cancer generation in human. Some new aspects of the cancer pathogenesis such as DNA methylation, and micro RNAs are being increasingly recognized as most valuable ailments.

According to International Agency for Cancer Research (2008) there are approximately 12.7 million new cancer cases with 7.6 million cancer deaths occurred, especially in the ill developed regions [5] (Fig 2). In case of lung cancer and pancreatic cancer, it was reported that mortality rates are still maintained almost in unchanged manner compared to 40 years ago [6].

Abnormalities in gene regulations found in cancer cells typically affect general classes of genes and their expression levels. Oncogenes that promote cancer are typically activated in cancer cells giving new characters like uncontrolled cell growth and division, inhibition of programmed cell death or apoptosis, and induced abnormal tissue environments. Today, breast Cancer is one of the most dangerous and life-threatening disease. In UK, on an average, one woman out of nine will progress breast cancer in their lifespan. There are several factors associated with the breast tumor, like use of alcohol, irregular body movement, family history, abnormal lifestyle, gender, improper diet, and endocrine orchestra. For last 10 years lung cancer has been the most common cancer type spreaded throughout the world. In 2014 there were 46,403 new lung cancer cases diagnosed in the UK. In England reports suggested that all stages of lung cancer has 1-year survival rate that improved from 24.5% in 1995–99 to 36.7% currently [7]. The American Cancer Society projected nearly 1,59,390 deaths from lung cancer in 2009,

\* Santanu Debnath

✉ santanudebnath11@gmail.com

<sup>1-2</sup> Department of Zoology, Brahmananda Keshab Chandra College, Kolkata - 700 108, West Bengal, India

accounting for about 28% of total cancer deaths [8]. Tobacco smoking is the main cause for lung carcinogenesis, specifically NSCLC is induced due to long-term cigarette-smoking in human, although passive smoking can affect the secondary smokers [9-10]. Polycyclic aromatic hydrocarbons (PAHs) are the most dangerous environmental pollutants that are mainly found in tobacco smoke, responsible for lung cancer progression [11].

has been associated with reduced risk of death in them. But, adjuvant chemotherapy or adjuvant radiotherapy, has not any significant improvement capacity of the survival rate after surgery [17]. Due to the violent behavior of this disease, less than 20% of these patients are expected to be alive in five years, confirming that this disease remains a public health problem in the country. Complete surgical resection is now the only therapeutic alternative that capable of providing a chance of cure gastric adenocarcinoma [18] (Fig 3).

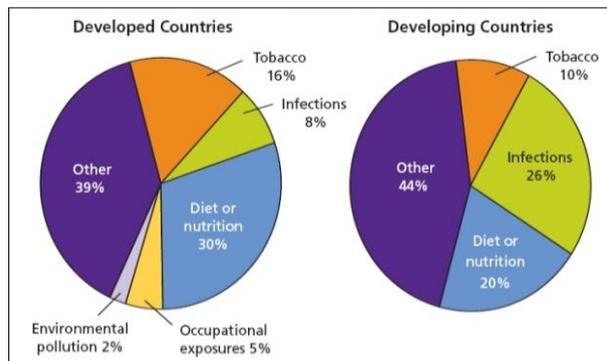


Fig 1 Proportion of cancer causes by major risk factors and level of economic development (www.cancer.org/canceratlas)

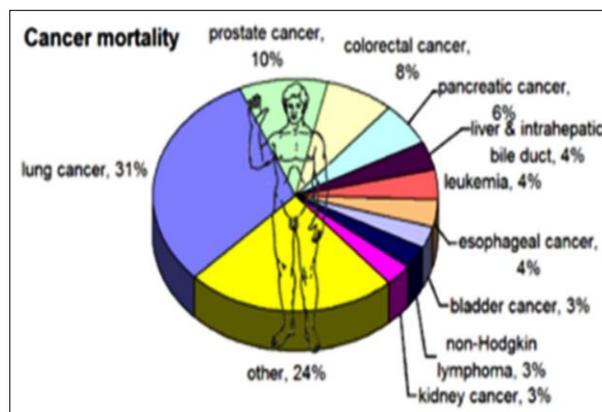


Fig 3 Types of cancers and their mortality rate (https://commons.wikimedia.org/wiki/File:Most\_common\_cancers\_-\_male,\_bymortality.png)

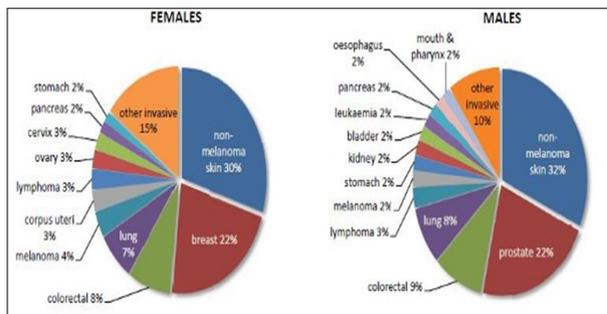


Fig 2 Relative frequency of the main invasive cancers diagnosed, 2009-2019 (https://seer.cancer.gov/statfacts/html/all.html)

Benzo[a]pyrene (BaP) is one of the reputed PAHs commonly found in cigarette smoke, responsible for lung tumour formation and causing inflammation in smokers [12]. Recent studies proposed that prostate cancer incidence can accelerate much faster than brain cancer [13-14]. Colorectal cancer (CRC) is the commonest malignancies, ranking third in the world among both males and females in relation to mortality. According to the data from Globocan, 2012, there are almost 1.6 million new CRC cases and 694,000 people died from CRC each year. Age, family history, gender, region, personal history, etc. are the major risk factors for the occurrence and progression of colorectal cancer. Genetical mutations including microsatellite instability (MSI), BRAF mutations, PIK3CA mutations, KRAS mutations and high-degree CpG island methylator phenotype are some major components involved to cause CRC [15]. Prostate cancer (PCa) is a common cancer type in elderly men. The occurrence of PCa is different in different countries, and the general mortality rate of prostate cancer reaches 1–2% now. The mechanisms of PCa progression have been explored, and key progresses have been made in the treatment of PCa [16]. Gastric cancer diagnosed at an early stage will often respond to surgical involvement with curative purpose. Gastric cancer patients are now treated with adjuvant chemotherapy as a postoperative modality that

Surgery is the most common treatment policy for patients with stage I and II of different cancer types, whereas patients with later stages are treated with combinations of surgery, chemotherapy, and radiation therapy [19]. Indication of malignancy can be suspected from some symptoms associated with radiographic imaging abnormalities followed by histological examination of a tissue biopsy. If detected in the initial stage most cancers can be successfully treated and some of these can be cured depending on the specific type of cancer, location of it and stage with the orthodox mode of treatment generally using a combination of surgery, chemotherapy and radiotherapy. However, success of cure of cancer is extremely poor if has advanced to a certain stage where it fails to respond to any kind of orthodox treatment. In orthodox regimen, advanced stages of cancer are often treated with some different drugs including cisplatin or carboplatin or in combination with paclitaxel, gemcitabine, etoposide, docetaxel, or vinorelbine, etc. which have significant side-effects on normal cells [20]. Most dreaded cancer types are hardly responding to such conventional chemotherapies due to mutations at p53, KRAS like major regulators involved in cell signaling that makes it resistant to chemotherapy [21]. As both chemotherapies and radiation therapies have deadly side-effects on normal cells, a search is on to find out some possible ways that could avoid these by using some alternative therapies that are equally effective with little or no side-effects.

Ancient reports gave the idea that there are different anticancer formulations published in ancient and modern medicinal books that should provide a useful guide along with clinical evidences for the recognition of new anti-cancer components. Alternative medicines used among cancer patients in Western countries is nearly 40%, whereas in Asia it is nearly 55.0%, in Singapore 56.0%, in Thailand 60.9%, 71.5% in Turkey, 97% in China, 57.4% in Korea,

98.1% in Taiwan, 56.6% in India and 59.0% in Brunei Darussalam. Bangladesh has developed a regular practice of use of alternative medicine that is rooted in their cultural heritage and constitutes an integral part of the culture of the common people of this country [22]. Now a days, different herbal therapies are commonly used by self-prescription to manage the common illness like anxiety, arthritis, colds, coughs, constipation, fever, headaches, infections, insomnia, intestinal disorders, premenstrual syndrome, stress, ulcers, weakness, etc. Some of the more common herbs in use today are echinacea, garlic, ginseng, goldenseal, ginkgo, saw palmetto, aloe vera, etc. [23]. All the previously described traditional medicinal systems are included under complementary and alternative medicines (CAM) regimen. The main advantage of CAM modalities is to use in a low price but effective with lesser side-effects [24]. Now a days all traditional medicinal plant extracts and their active components are introduced in modern clinical research for establishing their scientific roles in cancer treatment. CAMs including acupuncture, homeopathy, aromatherapy, Ayurveda, Unani, etc. are now getting more importance to cure many hardly cured diseases including cancer for more than 15 years and successfully got economical, medical, and sociological importance [25-26].

#### *Various organic and inorganic mediators involved in cancer remediation*

Recent studies have suggested that consumption of different fruits and vegetables are protective against cancers [27]. The World Cancer Research Fund and the American Institute for Cancer Research have concluded that carotenoid-containing, selenium-containing and quercetin containing foods are likely protective against cancer [3]. A local study has highlighted the defensive efficacy of cruciferous vegetables particularly in smokers [28]. Other than tobacco inducing lung carcinogenesis, researchers have also focused on cooking fumes, smoke emissions from incense [29], mosquito coils [30] and wood smoke [31] that are some other possible sources of carcinogens. Preserved meat-derived carcinogens during cooking or food-processing have also been studied [32]. There are different alkylating agents like dacarbazine and platinum compounds are widely used in the first- and second-line treatments of various tumors. Dacarbazine, a specific component was first synthesized by Shealy in 1962 and was approved by the Food and Drug Administration (FDA) in 1975 for treatment against melanoma and lymphomas. The so-called platinum compounds like cisplatin, carboplatin and oxaliplatin, are often used to treat several solid tumors were experimentally established [6]. Molecular biology is now growing with its advancement to detect the role of hormones in cellular growth and regulation of malignant cells in recent years. This research data clearly displayed that there are nearly 25% of tumors in males and 40% in females are known to have hormonal basis. Hormone-mediated treatment is now giving very fruitful results to treat cancer without hampering normal cells. Steroids are also hormone in nature, and such hormone-involved drugs are used to treat of cancers including leukemias, lymphoma, and multiple myeloma. Furthermore, corticosteroids are also used as antiemetics, that give much relief from nausea, vomiting and mitigate hypersensitivity after chemotherapy. Only when used in actual chemotherapy procedure, these drugs are called as chemotherapeutic drugs. Immunotherapy including both active immunotherapy and passive immunotherapies are

generally used to treat different diseases by manipulating the immune system. Self-limiting infectious diseases are easily controlled by traditional active vaccination strategies. Treatment of chronic infectious diseases and/or cancer is currently the main objective of immunotherapies that requires better understanding of the immune systems in terms of its regulatory mechanisms, identification of appropriate antigen, and optimization of the interaction between antigen-presenting cells (APC) and T cells. Dendritic cells are professional APC. They play a major role in the initiation and control of immune responses by regulating T and B lymphocyte activation. These cells are well positioned throughout the body in an immature state, surveying the tissues for invading pathogens, and are unique in antigen processing, and presentation in contrast with other antigen-presenting cells [33]. The prime target of any cancer therapy is to make a particular dose of therapeutic agents in the target tumor sites, thereby it can diminish the cancerous cells by minimizing the damage of normal cells. In respect of that it is crucial to make single agents with enormous potential to make an important contribution in cancer prevention, detection and treatment. In connection with that several ligand-targeted therapeutic strategies like radioimmune-therapeutics, immunotoxins, and drug immune conjugates, are being developed to prevail over the problems associated with conventional chemotherapeutic drugs, thereby providing additional tools for cancer treatment.

Although these innovative conjugated agents have some promising effects compared with conventional chemotherapeutic remedies, restrictions in their delivery process still remains a vital issue. Modern research practices targeted on nanotechnology that have a colossal impact on disease diagnosis and treatment. Cancer nanotechnology is now interdisciplinary research that connects the disciplines of chemistry, biology, engineering and medicine. The idea of giving more effective cancer treatments by inventing nanoscale mediated targeting provides an enthralling panacea for selective elimination of cancer cells without hampering normal cells. Nanomedicine has unbelievable potential to make far-reaching changes in cancer therapeutics and diagnostics by developing inventive biocompatible nanocomposites or drug delivery processes, which represent the most appropriate application of nanoparticles on target site. In the modern times, cancer researchers are the witness of effect on cancer cells by using nanocarriers (particularly size ranges from 10 nm to 100 nm). Two therapeutic nanocarrier- albumin and liposomes nanoparticles have been approved by the US FDA for clinical trials. The nanocarriers by using both passive and active targeting strategies, can bring about increased intracellular concentration of drugs in cancer cells that can manage to minimize the toxicity in normal cells [34]. The mechanism of metformin action is well studied in liver, adipose tissue, skeletal, and heart muscles. Glucose lowering effect is the main consequence of increased insulin sensitivity, reduced hepatic glucose production, and glucose use by muscles and adipocytes that results in decreasing insulinemia. Finally, the lipid favoring effects are due to increased fatty acid oxidation via phosphorylation of acetyl CoA carboxylase (ACC) by AMPK [35]. Recently bioluminescence imaging (BLI) technique is a very powerful application to localize tumors at different regions of human body. It can also quantify the cellular growth and monitoring the effects of therapy. The use of tumor cells expressing luciferase from firefly or other species have been

of particular utility as they provide a very sensitive signal with a short acquisition time that can be adapted for high-throughput techniques. D-luciferin, a substrate, administered at the patient's target site by intraperitoneal injection, and is oxidized by the endogenous luciferase when it reaches the tumor cell, resulting in photon emission. Although there are clear advantages for tumor characterization with this technique, several challenges and drawbacks exist [36].

#### Cancer and alternative remedies

*Scutellaria barbata* (SB) is a medicinal plant found in the Chinese Pharmacopoeia, contains flavor compounds like scutellarein, scutellarin, carthamidin, isocarthamidin, and wogonin. A diterpene substance called neo andrographolide and a cytotoxic constituent were also separated from *Scutellaria barbata* herb [37]. The anticancer property of SB extract was experimented in human lung cancer cell line-A549. Present study revealed the anticancer property of green tea (*Camellia Sinensis*) on different cancer types including esophagus, forestomach, lung, liver, duodenum, pancreas, colon, and breast. Recent study reported the anti-inflammatory properties of the flowers of the plant *Calendula officinalis*, commonly known as "Marigold", now are used in the West and in Asia [38]. *Calendula* is commonly to treat acute dermatitis in cancer patients undergoing postoperative irradiation. Its cytotoxic and anticancer efficacy on tumor cell lines in both *in vitro* and *in vivo* were established 20 years ago [39]. *Ganoderma lucidum* is very reputed mushroom to manufacture different products by Shanghai Green Valley Pharmaceuticals in China. Chinese literature suggests that *Ganoderma lucidum* contains anticancer property. It has some polysaccharides components that has active anti-tumor efficacy that are under investigation on human colorectal cancer cells, *in vitro* and *in vivo*. Huanglian is an herb in China commonly used for the preparation of herbal tea from its roots for several thousand years. Recent studies revealed that Huanglian is used to cure several inflammatory problems accompanied by high fever. Sulforaphane (SFN), is a dietary isothiocyanate compound found as a precursor glucosinolate in cruciferous vegetables such as brussels sprouts, cauliflower, and broccoli. Recent studies established its potent anticancer efficacy [40]. The bark extracts of *Cinnamomum cassia* tree contain several active components like tannin, mucus, essential oils (cinnamic aldehyde and cinnamyl aldehyde), and carbohydrates. According to recent reports this plant extract has different biological functions including antimicrobial, anti-oxidant, anti-diabetic effects, anti-inflammation, and anti-tumor efficacy [41]. *Chelidonium majus* L. is a very common medicinal plant generally used against differential diseases in European countries. Crude extracts of root, shoot and leaves of *Chelidonium* have different isoquinoline alkaloids like chelidonine, sanguinarine, berberine, chelerythrine and coptisine. Both crude extracts and purified compounds of *C. majus* have been reported to exhibit anti-viral, antimicrobial, anti-inflammatory, anti-tumor properties both *in vitro* and *in vivo* [42]. In the homeopathic treatment, various micro doses or potencies of *Chelidonium* herb extract are commonly used against several forms of liver disorders, including liver cancer with good effect.

Berberine is a well-known isoquinoline alkaloid found in the stem bark, roots, and rhizome of a number of important medicinal plants including *Berberis vulgaris*, *Berberis aquifolium*, *Berberis aristata* and *Tinospora*

*cordifolia* etc. Berberine is commonly used as antiarrhythmic, anti-diarrheal, and antitumor agent. Sulforaphane is another isothiocyanate first isolated from broccoli, is now reputed for its anti-cancer potential. Ursolic acid (UA) is a pentacyclic triterpene compound found in *Oldenlandia diffusa* and *Radix actinidiae*. Recent studies revealed that UA can modulate activities of DNA polymerase and DNA topoisomerase and can decrease the rate of cell proliferation. Moreover, UA can induce apoptosis in tumor cells by increasing the level of intracellular calcium ion and downregulating the expression of FoxM1 [16]. Folfiri, a combination therapy consisting of 5-FU, levoleucovorin and irinotecan, is one of the current standard chemotherapy alternatives for advanced CRC. *Emblica officinalis* Gaertn plant is originally native to India, is also found in Uzbekistan, Sri Lanka, Pakistan, China, South-East Asia, and Malaysia today. All parts of this plant are now used to treat differential cancers [5]. Danthron (1,8-dihydroxyanthraquinone) is a naturally occurring component that was isolated from the rhizome and root of *Rheum palmatum* L., is medicinally used in cancer treatment as an adjuvant and as a phytochemical immune modulator [43]. The dried tuber of *Typhonium giganteum* is published in the Chinese Pharmacopoeia as an important traditional Chinese medicine named Baifuzi [44]. Recent studies suggested that chemical components of *T. giganteum* tubers contains  $\beta$ -sitosterol-D-glucoside,  $\beta$ -sitosterol, cerebroside, dl-inositol, etc. that had potent anticancer activity, both *in vitro* and *in vivo*. It was also reported that the aqueous extract from *T. giganteum* tubers can induce apoptosis in SMMC-7721 cells via cell cycle arrest in S phase. Sulforaphane is another common isothiocyanate isolated from saga broccoli has anti-cancer potential via apoptosis induction [30]. *Artocarpus altilis*, known as breadfruit, is a widely known food source but is also commonly used as a folk medicine in Indonesia called Sukun. Medical research proposed that the leave extract of Sukun is used to treat hypertension liver cirrhosis, and diabetes [45]. Recent studies published that the ethylacetate extract of the Sukun leaves had cytotoxic effects on some human cancer cell lines like human colon carcinoma (SW-480 cells), human lung adenocarcinoma (SPC-A-1 cells), and human hepatocellular carcinoma (SMMC-7721 cells), that indicating the anti-cancer potential of this Sukun leaf extract [1].

Anticancer potential of homeopathic medicines like Lycopodium, Chelidonium, etc. in treating p-dimethyl amino azobenzene induced and phenobarbital promoted hepatocarcinogenesis in mice was reported earlier [46]. Recent reports suggested that *Sabal serrulata* can significantly reduce the prostate tumour [47]. Some homeopathic remedies have significant efficacy to downregulate the progression of cancer cell proliferation and mortality too in rats injected with MAT-LyLu prostate cancer cells [49]. Hydrastis, a common homeopathic mother tincture and its different dilutions were found to extend the life span of ascites tumour bearing animals [50]. Ruta 200c, Hydrastis 200c, Lycopodium 200c like homeopathic dilutions originated from the herbs (Fig 4) can inhibit the cancer progression in N-nitrosodiethylamine (NDEA) induced hepatocarcinogenesis in rats. Pathak *et al.* [46] found Ruta 6c can inhibit glioma growth in brain cancer in rats.

Hesperidin, a flavanone, found mainly in citrus fruits has anti-inflammatory, antioxidant, prostaglandin-synthesis inhibition, anti-mutagenic activity, etc., [51]. It has been

reported that hesperidin has several health beneficial effects, including the inhibition of skin tumorigenesis and bladder carcinogenesis. Today silibinin is reputed for its chemopreventive and anticancer activity against skin, prostate, bladder, and colon originated cancer [52]. Recent studies reported that Silibinin can block different cytokine-induced signaling pathways that control inducible nitric oxide synthase (iNOS) expression in A549 cells, and can regulate the growth of A549 xenografts, *in vivo*. Gallic acid (3,4,5-trihydroxybenzoic acid, GA), a naturally occurring plant phenol can induce the apoptosis in human leukemia HL60RG cells, *in vitro* and also has scientific evidence to act on human stomach cancer and colon adenocarcinoma cell lines in a positive way [53-54].



Fig 4 Common herbs are used as homeopathic remedies against differential cancer

The drugs discovery, especially in oncology is a versatile field and to discover several new approaches every year. There has been a rapid growth in the number of drugs available in the biological, genetical and molecular fields particularly after the Second World War. In that time there is not only the increment in the number of available drugs, but also an increment in the efficacy of the treatments was also there that consequently led to a notable upliftment in the survival and quality of life of the infected people. There are different clinical trials currently underway to manufacture new, effective drugs for the treatment of different tumors of different origins. This review work contains a brief survey on the use of complementary and alternative therapies on cancer patients in the recent era. This study gives current evidence of the use of alternative modalities, their types, facts behind use or non-use, merits and demerits, if any, cost-effectiveness and specific side-

effects. It is evidenced that this alternative treatments on differential cancer patients by using various homeopathic preparations and herbal extracts has some positive responses. It is also reported that more than one-third (35.9%) of the cancer patients are now under the treatment of these alternative modalities, with some variations in doses in different countries. So, all the traditional medicinal plant and herb extracts and separated active components of them have improved the research to find out and evaluate their scientific impacts to mitigate cancer and successfully gained economical, medical and sociological importance [55]. Apoptosis induction is now one of the major healing approaches to reduce and inhibit the cancer development through some signaling mechanisms. It is now clear that complementary and alternative therapies especially Ayurveda and homeopathic remedies have some positive impacts on differential cancer cells *in vitro* and *in vivo*. According to the hypothesis proposed by [56] based on direct and indirect evidences demonstrated that one of the major mechanisms through which the homeopathic drugs act, might be by the upregulation or downregulation of gene expressions [57]. But till today more in-depth research works are required to arrive at a definite conclusion about the precise mechanisms of action of the homeopathic drugs in its different states. Going by the proverb that “there is no smoke without fire”, it can safely be said that this is going to bring more confrontations between the believers and nonbelievers. More research activities are warranted on this ‘controversial’ science, so that more evidences to unravel its scientific intricacies may come out.

## CONCLUSION

Analysis of the degree of differences in various research data presented in this review work can be claimed that complementary and alternative therapies brought in perceptible modulatory changes in the parameters of study selected. Now a days many of natural components have been confirmed to have major advantages and have potential use for cancer treatment. The present explored natural products that have been used or have great potential to use against differential cancers are described in this review. Taking into considerations of all aspects of this major study, it was revealed that modern alternative treatments form elicited positive response as revealed from the modulatory effects shown by the living organisms. Regarding the mechanism of action, there exist many views and studies were warranted to understand the possible mechanism involved and could act by regulation of expressions of some relevant genes. In conclusion, present research work has clearly shown that alternative remedies opening up possibilities of increasing survivability and longevity of differential cancer patients who are facing some difficulties in conventional treatments, giving them a better way of life with reduction in chemotherapeutic toxicity.

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