Anticancer Plants

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The rising burden of cancer worldwide calls for an alternative treatment solution. Herbal medicine provides a very feasible alternative to western medicine against cancer. This entry reviews the selected plant species with active phytochemicals, the animal models used for these studies, and their regulatory aspects. This study is based on a meticulous literature review conducted through the search of relevant keywords in databases, Web of Science, Scopus, PubMed, and Google Scholar. Twenty plants were selected based on defined selection criteria for their potent anticancer compounds. The detailed analysis of the research studies revealed that plants play an indispensable role in fighting different cancers such as breast, stomach, oral, colon, lung, hepatic, cervical, and blood cancer cell lines. The in vitro studies showed cancer cell inhibition through DNA damage and activation of apoptosis-inducing enzymes by the secondary metabolites in the plant extracts. Studies that reported in vivo activities of these plants showed remarkable results in the inhibition of cancer in animal models.

Keywords: cancer ; apoptosis ; herbs ; cell lines ; in vivo

1. Introduction

The burden of cancer rose to 18.1 million new cases and 9.6 million deaths in 2018. With 36 different types, cancer mainly affects men in the form of colorectal, liver, lung, prostate, and stomach cancer and women in the form of breast, cervix, colorectal, lung, and thyroid cancer [1]. Treating cancer has become a whole new area of research. There are conventional as well as very modern techniques applied against cancers. A variety of techniques i.e., chemotherapy, radiation therapy, or surgery are used for treating cancer. However, all of them have some disadvantages [2]. The use of conventional chemicals bears side effects and toxicities [3]. But as the problem persists, new approaches are needed for the control of diseases, especially, because of the failure of conventional chemotherapeutic approaches. Therefore, there is a need for new strategies for the prevention and cure of cancer to control the death rate because of this disease.

Herbal medicine has become a very safe, non-toxic, and easily available source of cancer-treating compounds. Herbs are believed to neutralize the effects of diseases in a body because of various characteristics they possess [4]. For instance, among the many anticancer medicinal plants, *Phaleria macrocarpa* (local name: *Mahkota dewa*) and *Fagonia indica* (local name: *Dhamasa*) have been used traditionally for the anticancer properties of their active ingredients [5][6]. Metabolites extracted from the plant material are used to induce apoptosis in cancer cells. Gallic acid as the active component was purified from the fruit extract of *P. macrocarpa* and has demonstrated a role in the induction of apoptosis in lung cancer, leukemia, and colon adenocarcinoma cell lines [7][8]. It is a polyhydroxy phenolic compound and a natural antioxidant that can be obtained from a variety of natural products i.e., grapes, strawberries, bananas, green tea, and vegetables [9]. It also plays a critical role in preventing malignancy transformation and the development of cancer [10]. Similarly, other compounds such as vinca alkaloids, podophyllotoxin, and camptothecin obtained from various plants are used for the treatment of cancer.

With the advancement in the industrial sector and industrial medicine, the use of herbs was forgotten for a long period of time [11]. Hurdles regarding natural compounds are reduced because of the advent of new techniques and interest has been developed in the use of such natural ingredients in the pharmaceutical industry [12][13]. It has been estimated by the world health organization that 80% of the world is using traditional treatment methods [14]. Understanding of the effects or actions of herbs on various targets comes with the help of modern biomolecular science which recognizes some important properties i.e., anticancer, anti-inflammatory, and anti-virus. With the increasing understanding of the effects of such herbal medicine, their effects against different types of cancers have also been identified. For instance, hepatocellular carcinomas (HCC) are considered as the fifth most common malignancy in the world with increasing incidence [15][16]. Many studies have been performed on the treatment and prevention of using herbal medicine against HCC in which it is shown that all phases of HCC such as initiation, promotion, and progression could be affected by components of herbs [17][18].

However, as far as herbal compounds are considered as drugs, it is erroneously believed that they have no issues in terms of safety and side effects. There are hundreds of species of plants that are toxic to health. In the same way, there are many compounds in otherwise friendly plants that cause cytotoxicity. Based upon testing it has been proved that even anticancer plants result in cytotoxic effects [19].

Herbs are regulated under the “dietary supplement health and education act” as a dietary supplement in the United States of America. This review highlights the mechanism of some very important anticancer plants, the research related to their mechanism of action, their active ingredients, and the guidelines in place for their regulations.

2. Selected Plants and Their Anticancer Activity

Research so far has tested the anticancer activity of a plethora of plants and plant-based compounds. Some of these plants and their compounds prove to be very effective against one or more types of cancers. Based on their activities, the following plants are selected for the in vitro and in vivo anticancer activities of their compounds. The rest of the important plants shortlisted for their activities are presented in Table 1 along with their activities.

2.1. Artemisia annua

The genus Artemisia, widespread in Europe, Asia, North America, and South Africa has approximately 400 species worldwide [20]. Plants of the genus were used for centuries in classical medicine [21]. *Artemisia annua* is an annual short-day plant that belongs to family Asteraceae, having a brownish rigid stem. *A. annua* is known as sweet wormwood (Chinese: qīnghāo) and “dona” in the Urdu language in India and Pakistan [8]. *A. annua* was used by old Chinese for the preparation of anti-malarial drugs known as artemisinin (**Figure 1**). Having a unique ability of environmental adaptation it consistently resists insects and pathogens [22].

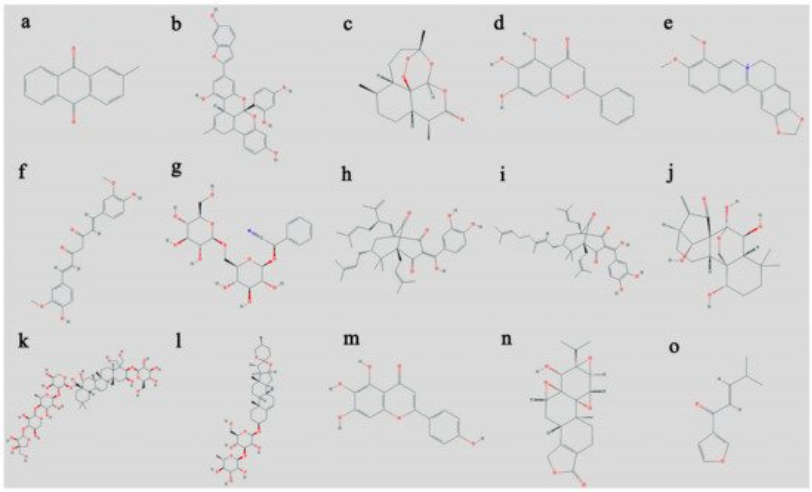

Figure 1. Structural representation of important anticancer secondary metabolites from plants. The structures are adapted from NCBI cited as National Center for Biotechnology Information. PubChem Database. (**a**) 2-Methylanthraquinone, Compound identification number (CID) = 6773; (**b**) albanol A, CID = 44567218; (**c**) artemisinin, CID = 68827; (**d**) baicalein, CID = 5281605; (**e**) berberine, CID = 2353; (**f**) curcumin, CID = 969516; (**g**) D-amygdalin, CID = 656516; (**h**) garcinol, CID = 5281560; (**i**) oblongifolin A CID = 53364454; (**j**) oridonin, CID = 5321010; (**k**) platycodin D, CID = 162859; (**l**) polyphyllin C, CID = 44429637; (**m**) scutellarein, CID = 5281697, and (**n**) triptolide, CID = 107985. (**o**) isoegomaketone, CID = 5318556; https://pubchem.ncbi.nlm.nih.gov/compound/ (accessed on 18 July 2019).

A. annua also synthesize scopoletin and 1,8-cineole compounds. Similarly, semi-synthetic derivatives of artemisinin are also generated such as arteether, artemether, and artesunate. Artesunate has been studied to be a very effective anticancer compound. Efferth [23] studied the effect of artesunate on 55 different cancer cell lines including leukemia, melanoma, lung cancer, colon cancer, renal cancer, ovarian cancer, and tumors of the central nervous system. They suggested that artesunate was most effective against leukemia and colon cancers. Furthermore, it was observed through these studies that the artesunate was more active than the drugs used for such cancers.

The stem and leaves *A. annua* were subject to extraction with the help of 80% ethanol and water. Several quantitative phenolic compounds from *A. annua* were identified using high-performance liquid chromatography (HPLC). The extracts were tested against HeLa and AGS cell lines. The cell growth inhibition activity of stem extracts was lower compared to leaf extracts. The ethanolic extracts of leaves lead to growth inhibitions (57.24% and 67.07%) in HeLa and AGS cells, respectively at a concentration of 500 mg/mL. HPLC analysis showed that the amount of phenolic acids was lower in stem

extract than in leaves extract of *A. annua*. It was concluded from the data that the antioxidant and anticancer capacity was the result of phenolic compounds as well as unidentified compounds within *A. annua* [24].

2.2. Coptis chinensis

Coptis chinensis, the Chinese goldthread, is a herb used as a traditional medicine in China thus officially enlisted in the Chinese pharmacopeia [25]. It is widely known for its traditional use against various diseases like diarrhea, dysentery, acute febrile, and supportive infections. The organic extract of *C. chinensis* possesses anti-inflammatory and anti-oxidant properties [26][27]. *C. chinensis* extract has wide use in the treatment of cholera, dysentery, diabetes, blood and lung cancer because of its strong antibacterial activity [28]. *Coptis* genus contains the most important and active components, such as an alkaloid i.e., berberine (**Figure 1**). Berberines alkaloids are used frequently as criteria in the quality control of *Rhizoma coptidis* (Huang Lian) products and lead to the apoptosis of human leukemia HL-60 cells by down regulating nucleophosmin/B23 and telomerase activity.

2.3. Curcuma longa

Curcuma longa (Turmeric) belongs to the ginger family Zingiberaceae. It is a rhizomatous herbaceous perennial plant [29]. It is naturally found in Southeast Asia and the Indian subcontinent. These plants are annually collected for their rhizomes and are then propagated from some of those rhizomes [30]. *C. longa* possesses a broad range of pharmacological activities including anti- HIC (human immunodeficiency virus), anti-inflammatory, antioxidant effects, nematocidal and anti-bacterial activities.

Curcumin, the main component of *C. longa*, plays an important role in the therapeutic activities of *C. longa* [31]. Curcumin shows anticancer and anti-inflammatory activities as reported by many different studies. Cyclooxygenase (COX)-2 plays a vital role in the formation of colon cancer. In a study conducted by Goel et al. [32], the HT-29 colon cancer cells of humans were treated with different concentrations of curcumin to study the effect of curcumin on the expression of COX-2. The cell growth of HT-29 cells was inhibited by curcumin in a concentration- and time-dependent manner. Curcumin affected COX-2 by inhibiting its mRNA and protein expression, but no such inhibitory effect was found against COX-1. From this data, it can be suggested that the in vitro growth of HT-29 cells is significantly affected by a non-toxic concentration of curcumin. Curcumin may thus play an important role in the prevention of colon cancer. Furthermore, the anticancer effects of curcumin on human breast cancer cell lines (MCF-7) were assessed through lactate dehydrogenase and 3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H-tetrazolium bromide assays to assess cytotoxicity and cell viability, respectively. The results showed that curcumin induced cytotoxicity and inhibited cells in a time- and concentration-dependent manner. This was observed through increased caspase 3/9 activity and induction of apoptosis. The results also indicated that curcumin downregulated miR-21 the expression of miR-21 in MCF-7 cells by upregulating the PTEN/Akt signaling pathway [33].

2.4. Fagonia indica

Fagonia indica, locally known as “dhamasa” is a flowering plant and belongs to the family of caltrop, Zygophyllaceae [34]. Members of Fagonia genus are known for their use as traditional medicine and are found effective in the treatment of many skin problems [35]. Traditionally, it was also used as a medicine for curing cancer as well as ailments resulting from poisons [5]. Amino acids and proteins [36], flavonoids [37], alkaloids [38], saponins [39], and terpenoid [40] are the phytochemicals found in the Fagonia species. *F. indica* is found to have liver protective [41] and antioxidant properties as well [42].

The aqueous extracts of *F. indica* have been found very effective against different types of cancer specifically breast cancers. For instance, Waheed et al. [43] performed bioactivity-guided fractionation to isolate the active and potent fraction of the *F. indica* extract. The activity was assessed against three cancer cell lines: MCF-7 estrogen-dependent breast cancer, MDA-MB-468 estrogen-independent breast cancer, and Caco-2 colon cancer cells (**Figure 2**). The results through different pieces of evidence such as the activity of pan-caspase inhibitor Z-VAD-fmk, caspase-3 cleavage, and DNA ladder assays suggested that apoptosis was stimulated in MDA-MB-468 and Caco-2 cells. Furthermore, a new steroidal saponin glycoside caused necrosis through cell lysis in MCF-7 cells. Similarly, Lam et al. [44] also demonstrated significant activity against breast cancer cells line MCF-7 through an aqueous extract of *F. indica*.

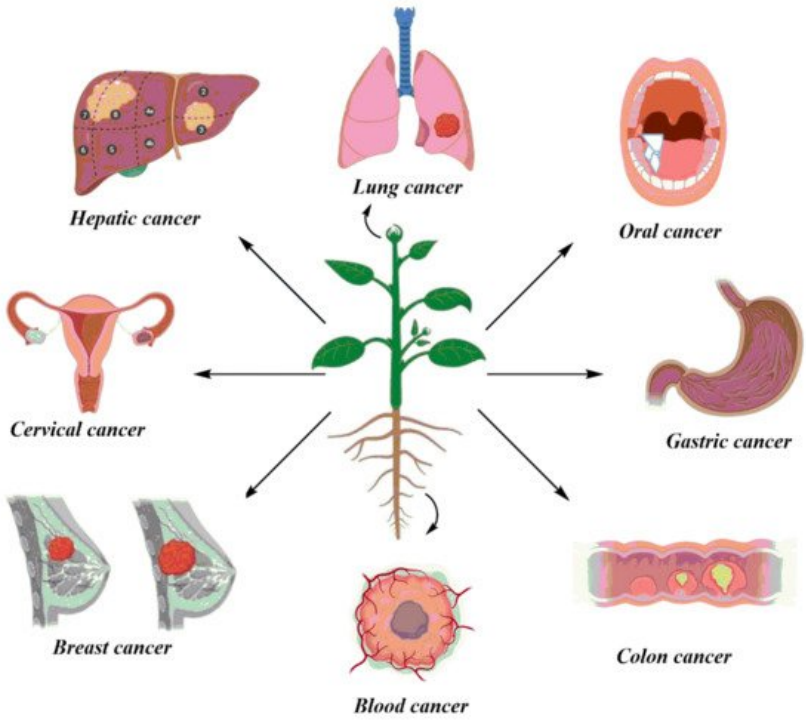

Figure 2. Illustration of activity of plants against several types of cancers. The icons were taken from Biorender illustrator and constructed through ChemBiodraw v14.0.

2.5. Garcinia oblongifolia

Garcinia oblongifolia (Lingnan Garcinia) belongs to the family of Clusiaceae and has a wide range of pharmaceutical activities. The important metabolites of the *G. oblongifolia* species; polyisoprenylated benzophenones and xanthones have anticancer, antioxidant, antifungal, apoptotic, and anti-pathogenic properties [45][46]. In vitro study showed that the bark of *G. oblongifolia* contains important secondary metabolites including oblongifolin A–G, oblongixanthones A–C along with other important compounds. These metabolites showed maximum apoptotic activities in HeLa-C3 cell lines and cytotoxic properties in the cervical cancer cells [47][48]. Li et al. [49] isolated about 40 different compounds from fruit, leaves, branches, and other parts of *G. oblongifolia*. They noted very high cytotoxic activities of these metabolites in the tested MCF-7 breast cancer cell line. However, they found the higher anti-cytotoxic activity of branch as compared to other plant parts. A small vacuole body formation was found at a low bark concentration of 0.250 g/mL. The vacuole size was increased at high concentrations of 500 g/mL and 1000 g/mL. The leaf part showed mild vacuole formation at a high concentration of 500 g/mL. Similarly, Feng, Huang, Gao, Xu and Luo [48] tested the pro-apoptotic activities of twenty different isolated compounds from *G. oblongifolia* in cervical cancer HeLa cells. Among all tested compounds the oblongifolins F and G, xanthone, nigrolineaxanthone T, and garcicowin B gave high pro-apoptotic properties at 10 µM concentration.

2.6. Garcinia indica

Garcinia indica, commonly known as kokum, is also an important medicinal plant that belongs to the Garcinia genus. The garcinol of *G. indica* shows positive activities in the experimental HT-29 and HCT-116 colon cancer cells along with normal immortalized intestinal cells (IEC-6 and INT-407). In another study, the fruit extract of *G. indica* was used for the isolation of garcinol. The garcinol at IC_{50} values (3.2–21.4 µM) for 72 h treatment shows strong inhibitory properties in all intestinal cells. The anticancer properties were higher in the cancer cells as compared to normal immortalized cells [50].

Similarly, Liao et al. [51] also observed a high tumor-inhibiting activity of *G. indica* in a human colorectal cancer cell line (HT-29). The garcinol at 10 µM concentration retarded the cell invasion activities several folds. The fruit extracts of *G. indica* has been shown very effective in the activation of caspase-3/CPP32 and the breakdown poly (ADP-ribose) polymerase (PARP) protein to inhibit leukemia in humans in the HL-60 cells [52]. These results indicated that garcinol (IC_{50} = 9.42 µM) shows strong growth inhibitory effects against human leukemia HL-60 cells.

2.7. Hedyotis diffusa

Hedyotis diffusa (Chinese: sheshecao) is a member of the family Rubiaceae. It is spread over the northeast regions of Asia. *H. diffusa* has been commonly used to cure inflammatory diseases i.e., urethritis, bronchitis, and appendicitis [53][54].

Because of the recent advances in pharmacological practices, this herb received importance for having antitumor properties and showed effective results in treating cancers of the liver, colon, lungs, brain, and pancreas [55]. *H. diffusa* contains important bioactive derivatives of polysaccharides, triterpenes, and anthraquinones [56][57].

Methyl anthraquinonesare, one of the bioactive compounds in *H. diffusa*, is responsible for apoptosis of many cancers. It shows apoptosis and inhibitory effect on the MCF-7 cell line of breast cancer via activation of the caspase-4/Ca^{2+}/calpain pathway when applied in a concentration of 18.62 µM for 24 h. It was observed that the S phase of the cell cycle and the percentage of the apoptotic cells were markedly increased when methyl anthraquinone was applied to MCF-7 cells [58]. Similarly, a concentrated extract of *H. diffusa* cause an inhibitory effect on the cervical cancer proliferation and induces apoptosis of Hela cells. Studies on the effect of *H. diffusa* ethanolic extracts on anti-colorectal cancer showed that these extracts cause an inhibitory effect on the Ct-26 cells by applying different concentrations (0.06 mg/mL, 0.08 mg/mL, 0.10 mg/mL and 0.12 mg/mL) with the rate of 35.46% to 71.84% [59].

3. In Vivo Studies of Anticancer Herbal Medicine: An Overview

The herbal medicines are tested both in vitro and in vivo. The anticancer activities of the various medicinal plants have been tested in vivo using different animal models (**Figure 3**). There are many studies available on in vivo experiments of the many different anticancer plants in mice models. For instance, dihydroartemisinin was reported to inhibit tumor tissue, increase the level of interferon-gamma (IFN-γ), and decrease interleukin 4 (IL-4) in tumor-bearing mice [60]. Similarly, artesunate, a derivative of artemisinin is also reported to be a promising drug against angiogenic Kaposi's sarcoma [61], growth inhibition of A549 and H1299 lung tumors by 100 mg/kg dose [62], the suppression of human prostate cancer xenograft [63] and the inhibition of leukemia growth in mice [64].

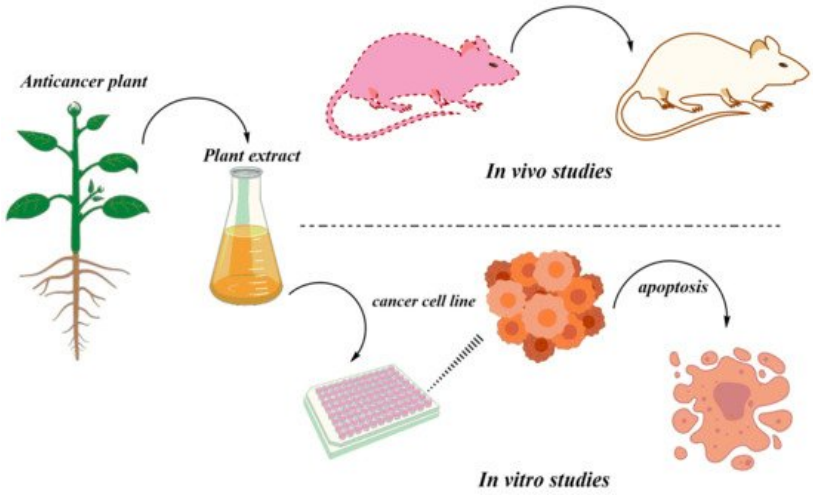

Figure 3. A depiction of general strategies applied for assaying extracts/phytochemicals from important medicinal plants for their anticancer activity both in vitro and in vivo.

Irradiation of C57BL/6 mice combined with a dose of 2 mg/kg twice a week was proved effective against lung carcinoma [65]. The effectiveness of berberine was enhanced when it was used in combination with other agents. Coptisine, another alkaloid of *Coptidis rhizoma* is proved to have anticancer effects when used in concentrations of 150 mg/kg against BALB/c nude mice by suppressing tumor growth and reducing cancer metastasis. The inhibition of the RAS-ERK pathway was suggested as the mechanism for this activity [66]. Another study was also performed on the nude mice on the HepG2 cells by applying the aqueous extract of *H. diffusa* which inhibits proliferation of cells in a dose-dependent manner, also delay S phase and arrest cells in G_0/G_1 phase [67].

Similarly, a high anticancer activity of SBT-A was found in transplanted tumor nude mice. Yang et al. [68] reported the anticancer activity of the polysaccharides isolated from *S. barbata* by 95-D Xenograft model. The results showed that polysaccharides give strong anti-proliferative activities against a 95-D cell line. It also lowered the expression of phospho-c-Met and other signaling elements like phospho-Erk and phospho-Akt. In vivo study also gave maximum antitumor activity by using a 95-D subcutaneous xenograft model. After one daily intraperitoneal injection for 3 weeks, the tumor growth was significantly decreased (47.72 % and 13.6%) at 100 and 200 mg/kg treatments. The ex vivo studies also showed that polysaccharides of *S. barbata* inhibit the phosphorylation of c-Met signaling pathway.

Furthermore, Li et al. [69] isolated a steroidal saponin from *P. polyphylla* which inhibited tumor growth in Lewis bearing-C57BL/6 mice and induced apoptosis in A549 cells. Results showed that steroidal saponin in concentration of 2.5, 5.0,

and 7.5 mg/kg showed significant inhibition rate of 26.49 ± 17.30%, 40.32 ± 18.91%, and 54.94 ± 16.48%, remarkably increased thymus and sleep indices, decreased inflammatory cytokines (TNF-α, IL-8, and IL-10). This in turn inhibited the tumor growth in C57BL/6 mice by reduced volume and weight of tumor. Nuclear changes, DNA condensation, chromatin fragmentation, and apoptosis are induced in A549 cells with a concentration of 0.25, 0.50, and 0.75 mg/mL steroidal saponin. Tumor growth inhibited by steroidal saponin was associated with decreased ROS, inflammatory response, and induction of apoptosis.

Furthermore, Wanga et al. [70] reported the effect of isoegomaketone from *P. frutescens* on Huh-7 hepatoma cell carcinoma and tumor-xenograft nude mice. Results showed that isoegomaketone inhibited cells and decreased tumor weight and volume. Isoegomaketone in the concentration of 10 nM/L decreased pAkt without affecting Akt. Hepatoma cell carcinoma tumor growth was suppressed by isoegomaketone from *P. frutescens* through PI3K/Akt signaling pathway blocking. *R. coptidis* is also showed anticancer activity in rats as suggested by the inhibition of cyclooxygenase 2 activity. The number of aberrant crypt foci in the rat colon was decreased by 54% after the administration of *R. coptidis* extracts [71].

Manjamalai and Grace [72] reported the apoptosis along with lowering angiogenesis and lung metastasis activities of the essential oils of *W. chinensis* by using B16F-10 melanoma cell line in C57BL/6 mice. The mice were injected with B16F-10 melanoma cells through the tail vein and treated with different doses of essential oil. A 50-µg essential oil concentration showed maximum cytotoxic activities with 65.17% lethality within 24 h. The numbers of apoptotic cells increased many times in experimental samples as compared to the control group. They also recorded high levels of important proteins like p53 and caspase-3 in essential oil-treated samples compared to other non-treated samples. They recommended this plant for the treatment and control of cancer.

In vivo activities of oridonin from *R. rubescens* showed a potent anticancer potential in the gallbladder [73]. When injected intra-peritoneally with a concentration of 5, 10, 15 mg/kg for 3 weeks to athymic nude mice, oridonin significantly inhibited NOZ xenografts growth. Oridonin also inhibited NF-κB nuclear translocation, increased Bax/Bcl-2 ratio, activated caspase-3, caspase-9, and PARP-1 which showed that the mitochondrial pathway is concerned with apoptosis mediated by oridonin.

Studies have reported anticancer activities of two artemisinin dimer, dimer-hydrazone (dimer-Sal) and dimer-alcohol (dimer-OH) and one monomer dihydroartemisinin (DHA) compared to the control against MTLn3 breast tumors in rats. Results of the study reported that dimer-Sal, dimer-OH, and DHA significantly suppressed tumors in rats compared to the control group. It was also observed that the dimers were more potent as compared to the monomers [74].

It is also reported that artemisinin is responsible for preventing breast cancer in rats treated with a single oral dose (50 mg/kg) of 7,12-dimethalbenz anthracene (DMBA) which is known for rapidly inhibiting the multiple breast tumors. After the feeding DMBA with 0–2% artemisinin to the target group and plain food in powdered form to the control group, both groups of experimental rats were monitored for breast tumors for 40 weeks. Oral artemisinin significantly reduced the development of breast tumors (57%) as compared to control fed (96%). The research indicates that artemisinin might be a potent cancer chemoprevention agent, having lesser side effects [75]. Similarly, oral administration of curcumin to rats reduced the level of Gp A72 (glycoprotein) by 73% hence lowering paw inflammation [76].

Tanaka et al. [77] observed activities of fruit extracts of *G. indica* in the azoxymethane (AOM)-induced colonic aberrant crypt foci in male model rats (F344). They found lower proliferating cell nuclear antigen index and high concentrations of glutathione S-transferase and quinone reductase. They also observed the maximum chemo-preventive activities of garcinol.

Besides mice and rats, there are many other animal models employed for studying anticancer activities. Zebrafish models are also employed for technical advantages including the ease of advanced genetic studies, expression of tumor in any organ and the striking resemblance to human malignancies [78]. Zhu et al. [79] used furanodiene which is a terpenoid isolated from *Rhizoma curcumae*, for their anticancer effects in zebrafish models. They observed that furanodiene showed anticancer effects in a pancreatic cell line (JF 305) and human breast cancer cells (MCF-7) transplanted into zebrafish. Furanodiene showed effective results through ROS production, anti-angiogenesis, apoptosis induction, and DNA strand breaks.

Similarly, the artemisinin type compound can have anticancer activities against different types of tumors including leukemia, carcinomas of breast, kidneys, lungs, and ovaries, lymphoma, melanoma, and brain tumors [23][80][81]. Currently, reports of in vivo activities of *A. annua* are accumulating. One study reported anticancer activities of *A. annua* against four animal models aged 10 including a male cat with malignant fibrosarcoma, a male dog with malignant mesenchymal

neoplasia, a female dog with breast cancer and another male dog with a malignant fibrosarcoma. The animals were treated with various doses of 150 mg/day (3 capsules), 450 mg/day (2 capsules), 450 mg/day (3 capsules), and 450 mg/day (2 capsules). All the animals showed complete reduction with no tumor relapse [82].

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