Role of Plant-Derived Active Constituents in Cancer Treatment and Their Mechanisms of Action

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Abstract: Despite significant technological advancements in conventional therapies, cancer remains one of the main causes of death worldwide. Although substantial progress has been made in the control and treatment of cancer, several limitations still exist, and there is scope for further advancements. Several adverse effects are associated with modern chemotherapy that hinder cancer treatment and lead to other critical disorders. Since ancient times, plant-based medicines have been employed in clinical practice and have yielded good results with few side effects. The modern research system and advanced screening techniques for plants’ bioactive constituents have enabled phytochemical discovery for the prevention and treatment of challenging diseases such as cancer. Phytochemicals such as vincristine, vinblastine, paclitaxel, curcumin, colchicine, and lycopene have shown promising anticancer effects. Discovery of more plant-derived bioactive compounds should be encouraged via the exploitation of advanced and innovative research techniques, to prevent and treat advanced-stage cancers without causing significant adverse effects. This review highlights numerous plant-derived bioactive molecules that have shown potential as anticancer agents and their probable mechanisms of action and provides an overview of in vitro, in vivo and clinical trial studies on anticancer phytochemicals.

Keywords: cancer; incidence; epidemiology; phytochemicals; mechanism; clinical trials

1. Introduction

Cancer is a challenging disease and is the main cause of mortality worldwide; however, its impact is not evenly distributed. The cancer burden in developed and underdeveloped countries has increased over time owing to a variety of factors, including aging and growing populations, rapid socioeconomic growth, and changes in the incidence of risk factors. Owing to the growth and aging of the world population, cancer is showing reduced survival rates in many countries [1,2]. Cancer is a complex disease involving uncontrolled growth and proliferation of cells in tissues, resulting in cell aggregation locally (tumor), and it can spread to an entire organ or even to other neighboring tissues systemically (metastasis) [3]. The uncontrolled cell behavior can be caused by genetic or epigenetic changes in oncogenes involved in cell proliferation or cell death regulation [4]. The incidence and mortality rates of cancer are continuously increasing. According to a study published in 2020, the global incidence of cancer cases was 247.5, whereas the mortality rate was 127.8 per 100,000 people. Developed countries, such as Japan, Australia, New Zealand, Germany, Canada, and France, topped the list in cancer incidence and mortality rates [2]. Furthermore, breast cancer had the highest incidence rate of 11.7%, while lung cancer had the highest mortality rate of 18% [5]. The worldwide estimated incidence and mortality rates of different cancers are shown in Table 1, and the percentages of incidence and mortality of different types of cancers are shown in Figure 1.
Table 1. Estimated worldwide incidence and mortality rates (per 100,000 people) of all cancer types in 2020.

| Continents     | Incidence | Rank | Mortality | Rank |
|----------------|-----------|------|-----------|------|
| Worldwide      | 247.5     | –    | 127.8     | –    |
| Asia           | 204.8     | –    | 125.2     | –    |
| Japan          | 813.3     | 1    | 332.2     | 3    |
| China          | 315.6     | 57   | 207.5     | 42   |
| India          | 96        | 121  | 61.5      | 122  |
| South Korea    | 449.2     | 42   | 172.8     | 56   |
| Europe         | 587.4     | –    | 261.1     | –    |
| Germany        | 750.2     | 4    | 300.9     | 10   |
| France         | 716.9     | 9    | 284.4     | 17   |
| Italy          | 686.8     | 13   | 289.0     | 15   |
| North America  | 693.2     | –    | 189.6     | –    |
| USA            | 689.3     | 12   | 185.0     | 54   |
| Canada         | 726.9     | 7    | 229.7     | 33   |
| South America  | 224.8     | –    | 109.1     | –    |
| Brazil         | 278.6     | 63   | 122.3     | 72   |
| Argentina      | 289.6     | 60   | 155.0     | 63   |
| Colombia       | 222.5     | 75   | 108.1     | 81   |
| Africa         | 82.7      | –    | 53.1      | –    |
| South Africa   | 182.4     | 83   | 95.8      | 87   |
| Morocco        | 160.8     | 93   | 95.5      | 88   |
| Ethiopia       | 67.3      | 158  | 45.1      | 155  |
| Australia      | 784.4     | 2    | 189.2     | 51   |
| New Zealand    | 745.2     | 5    | 217.9     | 38   |

Several pathways are involved in cancer development, including the VEGF receptor pathway that can activate the RAS/RAF/MEK/ERK pathway [6] and the fibroblast growth factor (FGF) receptor pathway that activates multiple downward pathways, including the PI3K/Akt/mTOR, RAS/RAF/MEK/ERK and signal transducer and activator of transcription (STAT) pathways [7]. Reactive oxygen species (ROS) can activate the Akt/mTOR and AMPK signaling systems to induce cancer [8]. Wnt/β-catenin also plays a role in the development of multiple cancers [9]. Some important cancer-causing pathways and targets of the anticancer activity of phytochemicals are presented in Figure 2.

Since ancient times, herbal medicines have been used in health care systems. Research conducted to confirm the effectiveness of these medicines led to the discovery and development of plant-based medications. Local communities use medicinal plants to treat most diseases owing to lack of access to modern medication. In the past few decades, increasing evidence has revealed the remarkable potential plant-based therapeutics. Compared with synthetic medicines, medical plants have therapeutic potential with fewer side effects and lower costs [10].

Phytochemicals are plant-derived secondary metabolites. Based on epidemiological, in vitro, in vivo, and clinical trial data, a plant-based diet can lower the risk of many chronic diseases (e.g., neurological diseases, cardiovascular disease, diabetes, and cancer) owing to the action of bioactive plant constituents or phytochemicals [11].
Figure 1. Incidence and mortality rates of different cancer types in 2020. Percent increases in incidence and mortality rates of different cancers are shown, with breast, lung, prostate, colorectal, and stomach cancers having the highest incidence and mortality rates. Cancers with low percent incidence and mortality rates are combined as miscellaneous cancers.

Despite significant progress in the prevention and treatment of cancer, major gaps still exist, and further improvements are warranted. Modern chemotherapy has several side effects that impede the progress of cancer treatment and lead to other serious health problems. The development of integrated research systems and advanced screening procedures for plant bioactive components has ushered in a new era of phytochemical discoveries for the prevention and treatment of complex diseases such as cancer. Bioactive compounds such as berberine, curcumin, crocetin, colchicine, gingerol, lycopene, kaempferol, resveratrol, vincristine, and vinblastine have demonstrated remarkable anticancer potential [4]. Using modern and novel research approaches, more plant-derived constituents might be discovered to prevent and treat advanced-stage cancer without significant side effects.

In this review, we highlight phytochemicals that have been reported as anticancer agents and their putative mechanisms of action in cancer treatment and summarize in vitro, in vivo, and clinical trial data on these phytoconstituents.
Figure 2. Important cellular mechanisms involved in cancer and mechanisms of action of phytochemical drugs. Growth factors, such as vascular endothelial growth factor and fibroblast growth factor, bind with their respective receptors, resulting in their phosphorylation, followed by the activation of downstream signaling pathways, such as the PI3K/Akt, PLCγ, and STAT pathways. Akt activates IKK, which is responsible for the activation of the NF-κB signaling and mTOR pathway; IKK exerts its effect on cells by regulating the hypoxia-induced factor. ROS activates the Akt and AMP-activated protein kinase (AMPK) pathways by inducing endoplasmic reticulum stress. AMPK activates the tumor suppressor transcription factor (FOX O) and inhibits the action of mTOR. Wnt proteins suppress glycogen synthase kinase-3β (GSK-3β) by binding to frizzled receptors, disrupting the β-catenin complex (destructive complex). β-catenin accumulates in the cytoplasm, translocates to the nucleus, and induces cell proliferation, which promotes cancer by activating Wnt-regulated genes. Different phytochemicals act on different targets to exhibit anticancer activity.

2. Methodology

Data Collection

Articles on phytoconstituents with anticancer activity were searched for using specific keywords such as “phytochemicals”, “plant-derived constituents”, “plant-based medicine”, “antitumor”, “cytotoxic”, “cancer epidemiology,” and “incidence” from online research databases such as PubMed, Web of Science, Medline, Google Scholar, and Science Direct and downloaded. The articles were entirely read, and data on phytochemicals with anticancer properties were collected and tabulated in Table 2.
Table 2. Plant-derived phytochemicals with potential anticancer properties, and their mechanisms of action.

| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type       | Study Type        | Targets and Mechanisms                                                                 |
|------|----------------|-----------------|-----------------------|--------------------|------------------|------------------|------------------|---------------------------------------------------------------------------------------|
| 1    | Allicin        | Thioester       | *Allium sativum*      | C₆H₁₀O₂S₂          | 162.3            | Lung cancer      | In vitro         | Downregulation of VEGF expression [12]                                                  |
|      |                |                 |                       |                    |                  | Gastric cancer   | In vitro         | Enhanced expression of p38 and cleavage caspase-3 [13]                                  |
|      |                |                 |                       |                    |                  | Oral cancer      | In vitro         | Upregulation of and cleaved caspase-3 [14]                                              |
|      |                |                 |                       |                    |                  | Brain cancer     | In vitro         | Elevation in Fas/FasL expression [15]                                                   |
| 2    | Aloperine      | Alkaloid        | *Sophora alopecuroides* | C₁₅H₂₄N₂          | 232.36           | Ovarian cancer   | In vitro         | Reactive oxygen species activation [16]                                                 |
|      |                |                 |                       |                    |                  | Thyroid cancer   | In vitro, in vivo| Suppression of Akt pathway and downstream B-cell lymphoma (Bcl-2) expression [17]       |
|      |                |                 |                       |                    |                  | Prostate cancer  | In vitro, in vivo| Inhibition of Akt and ERK phosphorylation [18]                                           |
|      |                |                 |                       |                    |                  | Bladder cancer   | In vitro         | Downregulation of Ras, p-Raf1 and p-Erk1/2 expression [19]                               |
|      |                |                 |                       |                    |                  | Colon cancer     | In vitro         | Inhibition of JAK/Stat3 and PI3K/Akt pathways [20]                                        |
|      |                |                 |                       |                    |                  | Bones cancer     | In vitro         | Suppression of PI3K/AKT signaling [21]                                                   |
| 3    | Alpinumisoflavone | Isoflavone   | *Derris eriocarpa*    | C₂₀H₁₆O₅            | 336.3            | Colon cancer     | In vitro         | Blockage of DNA repairing [22]                                                          |
|      |                |                 |                       |                    |                  | Esophageal cancer | In vitro, in vivo, ex-vivo | Uregulation of miR-370 and suppression of PIM1 signaling [23]                      |
|      |                |                 |                       |                    |                  | Brain cancer     | In vitro         | Suppression of glycolysis and cyclin D1 expression and activation of caspase-9 [24]      |
| 4    | Amygdalin      | Diglucoside     | *Rosaceae kernels*    | C₂₀H₂₂NO₁₁         | 457.4            | Bladder cancer   | In vitro         | Modulation of β1 or β4 integrin expression [25]                                        |
|      |                |                 |                       |                    |                  | Breast cancer    | In vitro         | Downregulation of Bcl-2, upregulation of Bax and p38 MAPK signaling pathways [26]       |
|      |                |                 |                       |                    |                  | Prostate cancer  | In vitro         | Activation of caspase-3 through downregulation of Bcl-2 and up-regulation of Bax [27]   |
|      |                |                 |                       |                    |                  | Cervical cancer  | In vitro         | Downregulation of Bcl-2 and upregulation of Bax protein [28]                            |
| 5    | Andrographolide | Diterpenoid     | *Andrographis paniculata* | C₂₀H₃₀O₅          | 350.4            | Colon cancer     | In vitro         | Increase intracellular ROS level [29]                                                   |
|      |                |                 |                       |                    |                  | Skin cancer      | In vitro         | Activation of JNK and p38 signaling pathway [30]                                        |
|      |                |                 |                       |                    |                  | Breast cancer    | In vitro, in vivo| Suppressing of COX-2 and VEGF pathway [31]                                               |
|      |                |                 |                       |                    |                  | Prostate cancer  | In vitro, in vivo| Facilitate DNA damage [32]                                                              |
|      |                |                 |                       |                    |                  | Bile duct cancer | In vitro         | Suppression of Claudin-1 via p-38 pathway [33]                                           |
|      |                |                 |                       |                    |                  | Ovarian cancer   | In vitro         | Upregulation of TIMP1 expression [34]                                                    |
| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|----------------|-----------------------|-------------------|------------------|-------------|-----------|-----------------------|
| 6    | Apigenin       | Flavonoid      | Matricaria chamomilla | C_{15}H_{10}O_{5} | 270.24           | Colon cancer | In vitro, in vivo | Inhibition of the Mcl-1, AKT, and ERK pro-survival regulators [35] |
|      |                |                |                       |                   |                  | Lung cancer  | In vitro, in vivo | Inhibition of NF-κB, AKT and ERK pathway [36] |
|      |                |                |                       |                   |                  | Liver cancer | In vitro, in vivo | Inhibition of PI3K/Akt/mTOR signaling [37] |
|      |                |                |                       |                   |                  | Pancreatic cancer | In vitro | Through G2/M cell cycle arrest [38] |
|      |                |                |                       |                   |                  | Breast cancer | In vitro | Inhibition of YAP/TAZ activity [39] |
|      |                |                |                       |                   |                  | Prostate cancer | In vitro, in vivo | Suppression of NF-κB/p65 expression [40] |
|      |                |                |                       |                   |                  | Bone cancer  | In vitro | Suppression of Wnt/β-catenin signaling [41] |
| 7    | Artemisinin    | Alkaloid       | Artemisia annua       | C_{15}H_{22}O_{5} | 282.33           | Colon cancer | In vitro and in vivo | Increase in ROS production [42] |
|      |                |                |                       |                   |                  | Kidney cancer | In vitro, in vivo | Inhibition of AKT signaling [43] |
|      |                |                |                       |                   |                  | Ovarian cancer | In vitro, in vivo | Suppression of AKT/ERK/mTOR pathway [44] |
|      |                |                |                       |                   |                  | Gallbladder cancer | In vitro, in vivo | Inhibition of ERK1/2 pathway [45] |
| 8    | Baicalein      | Flavonoid      | Scutellaria baicalensis | C_{15}H_{10}O_{5} | 270.24           | Lung cancer  | In vitro, in vivo | Suppression of VEGF, FGFR-2, and RB-1 pathways [46] |
|      |                |                |                       |                   |                  | Colon cancer | In vitro | Activation of caspase-3 [47] |
|      |                |                |                       |                   |                  | Bladder cancer | In vitro, in vivo | Inhibition of cyclin B1, MMP-2 and MMP-9 mRNA expressions [48] |
|      |                |                |                       |                   |                  | Pancreatic cancer | In vitro, in vivo | Increase caspase-3 and Bax, while decrease survivin and Bcl-2 expressions [49] |
|      |                |                |                       |                   |                  | Liver cancer  | In vitro | Suppression of PI3K/Akt pathway [50] |
|      |                |                |                       |                   |                  | Prostate cancer | In vitro | Inhibition of caveolin-1/AKT/mTOR pathway [51] |
|      |                |                |                       |                   |                  | Breast cancer  | In vitro, in vivo | Activation of PAX8-ASI-N activation [52] |
|      |                |                |                       |                   |                  | Ovarian cancer | In vitro, in vivo | Inhibition of YAP and RASSF6 expressions [53] |
|      |                |                |                       |                   |                  | Skin cancer   | In vitro, in vivo | Inhibition of glucose uptake and metabolism of tumor cells [54] |
| 9    | Berbamine      | Alkaloid       | Berberis amurensis    | C_{15}H_{10}N_{2}O_{5} | 608.7           | Blood cancer | In vitro | Uregulation of caspase-3 and downregulation of MDR-1 gene expression [55] |
|      |                |                |                       |                   |                  | Liver cancer  | In vitro, ex vivo | Inhibition of Ca2+/Calmodulin-dependent protein Kinase II expression [56] |
|      |                |                |                       |                   |                  | Ovarian cancer | In vitro, in vivo | Inhibition of Wnt/β-catenin signaling [57] |
| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|----------------|----------------------|------------------|-----------------|-------------|------------|------------------------|
| 10   | Capsaicin      | Capsaicinoid   | Capsicum annuum      | C18H27NO3        | 305.4           | Colon cancer | In vitro  | Inhibition of MEK/ERK signaling [58] |
|      |                |                |                      |                  |                 | Head & neck cancer | In vitro  | Inhibition of STAT3 activation [59] |
|      |                |                |                      |                  |                 | Breast cancer | In vitro, in vivo | Downregulation of FBI-1-mediated NF-kB pathway [60] |
|      |                |                |                      |                  |                 | Lung cancer   | In vivo   | Downregulation of MMP-2 and -9 levels [61] |
|      |                |                |                      |                  |                 | Prostate cancer | In vitro  | Increases protein light chain 3-II (autophagy marker) and ROS levels [62] |
|      |                |                |                      |                  |                 | Colon cancer  | In vitro  | Stabilization and activation of p53 [63] |
|      |                |                |                      |                  |                 | Esophageal cancer | In vitro  | Decrease hexokinase-2 (HK-2) expression [64] |
|      |                |                |                      |                  |                 | Skin cancer   | In vitro  | Downregulation of PI3-K/Akt/Rac1 pathway [65] |
| 11   | Cepharanthine  | Alkaloid       | Stephania cepharantha | C37H38N2O6       | 606.7           | Colon cancer  | In vitro  | Upregulation of p21Waf1/Cip1 pathway [66] |
|      |                |                |                      |                  |                 | Breast cancer | In vitro  | Inhibition of AKT/mTOR signaling [67] |
|      |                |                |                      |                  |                 | Ovarian cancer | In vitro  | Increases expression of p21Waf1 and decreasing expression of cyclins A and D proteins [68] |
|      |                |                |                      |                  |                 | Liver cancer  | In vitro  | Activation of JNK1/2 signaling and downregulation of Akt pathway [69] |
|      |                |                |                      |                  |                 | Liver cancer  | In vitro, in vivo | Inhibition of DNMT1 expression [70] |
|      |                |                |                      |                  |                 | Colon cancer  | In vitro  | Activation of PARP-1, and caspase-9 [71] |
|      |                |                |                      |                  |                 | Breast cancer | In vitro  | Upregulation of Bax and downregulation of Bcl-2 expressions [72] |
| 12   | Chlorogenic Acid | Ester         | Etlingera elatior    | C16H18O9         | 354.31          | Gastric cancer | In vitro, in vivo | Induce caspase-3-mediated mitochondrial apoptosis [73] |
|      |                |                |                      |                  |                 | Hypopharyngeal cancer | In vitro, in vivo | Inhibition of phosphorylated FAK/SRC complex and paxillin [74] |
|      |                |                |                      |                  |                 | Breast cancer | In vitro  | Inhibition of MMP-2 expression [75] |
|      |                |                |                      |                  |                 | Colon cancer  | In vitro  | Decrease in AKT phosphorylation [76] |
|      |                |                |                      |                  |                 | Lung cancer   | In vitro, in vivo | Disruption of microtubule assembly [77] |
|      |                |                |                      |                  |                 | Bladder cancer | In vitro, in vivo | Activation of caspase-3 and reduction in BubR1 and Bub3 expressions [78] |
|      |                |                |                      |                  |                 | Bone cancer   | In vitro  | Inhibition of NDRG1 [79] |
Table 2. Cont.

| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|-------------------|------------------|-------------|------------|------------------------|
| 15   | Corosolic acid | Tripernoid | Lagerstroemia speciosa | C_{30}H_{48}O_{4} | 472.7 | Lung cancer | In vitro, in vivo | Inhibition of VEGFR2 kinase activity [33] |
|      |                |                 |                       |                   |                  | Colon cancer | In vitro, in vivo | Inhibition of HER2/HER3 receptors’ heterodimerization [80] |
|      |                |                 |                       |                   |                  | Gastric cancer | In vitro | Activation of AMPK pathway [81] |
|      |                |                 |                       |                   |                  | Liver cancer | In vitro, in vivo, ex vivo | Inactivation of CDK19/YAP/O-GlcNAcylation pathway [82] |
|      |                |                 |                       |                   |                  | Prostate cancer | In vitro, in vivo | Activation of IRE-1/JNK, PERK/CHOP and TRIB3 [83] |
|      |                |                 |                       |                   |                  | Cervical cancer | In vitro | Downregulation of PI3K and Akt signaling [84] |
|      |                |                 |                       |                   |                  | Kidney cancer | In vitro | Induction of lipid ROS [85] |
|      |                |                 |                       |                   |                  | Breast cancer | In vitro | Increase in ROS production and decrease in VEGF concentration [86] |
|      |                |                 |                       |                   |                  | Bladder cancer | In vitro, in vivo | Upregulation of SQSTM1/P62, NBR1, and UBB expression [87] |
| 16   | Crocetin       | Carotenoid | Crocus sativus | C_{20}H_{32}O_{4} | 328.4 | Prostate cancer | In vitro, in vivo | Induce DNA damage and apoptosis [88] |
|      |                |                 |                       |                   |                  | Colon cancer | In vitro | Upregulation FAS/FADD death receptor [89] |
|      |                |                 |                       |                   |                  | Pancreatic cancer | In vitro, in vivo | Upregulation of Bax and downregulation of Bcl-2 protein [90] |
|      |                |                 |                       |                   |                  | Gastric cancer | In vitro, in vivo | Upregulation of caspase-3, -8 and -9 [91] |
| 17   | Cucurbitacin   | Triterpene | Cucumis sativus | C_{32}H_{46}O_{8} | 558.7 | Colon cancer | In vitro | Inhibition of Hippo-YAP Signaling Pathway [92] |
|      |                |                 |                       |                   |                  | Gastric cancer | In vitro, in vivo | Suppression of Akt expression [93] |
|      |                |                 |                       |                   |                  | Bile duct cancer | In vitro | Downregulation of pRB, cyclin D1 and cyclin E expression [94] |
|      |                |                 |                       |                   |                  | Breast cancer | In vitro | Inhibition of Stat3 and Akt signaling [95] |
| 18   | Curcumin       | Curcuminoids | Curcuma longa | C_{21}H_{20}O_{6} | 368.38 | Breast cancer | In vitro | Upregulation of PTEN/Akt signaling pathway [96] |
|      |                |                 |                       |                   |                  | Gastric cancer | In vitro | Suppression of PI3K/Akt/mTOR signaling pathway [49] |
|      |                |                 |                       |                   |                  | Oral cancer | In vivo | Suppression of NF-κB, and COX-2 expression [97] |
|      |                |                 |                       |                   |                  | Prostate cancer | In vitro | Downregulation of NF-xB, and CXCL1 and -2 expressions [98] |
|      |                |                 |                       |                   |                  | Colon cancer | In vitro | Inhibition of AMPK-induced NF-xB, uPA, and MMP9 activation [99] |
|      |                |                 |                       |                   |                  | Ovarian cancer | In vitro | JAK/STAT3 pathway inhibition [100] |
|      |                |                 |                       |                   |                  | Lung cancer | In vitro | Increase in FOXA2 expression [101] |
| 19   | Diosgenin      | Saponin | Dioscorea villosa | C_{27}H_{42}O_{3} | 414.6 | Breast cancer | In vitro | Downregulation of Skp2 [102] |
|      |                |                 |                       |                   |                  | Liver cancer | In vitro | Inhibition of Akt and upregulation of p21 and p27 expression [103] |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|------------------|------------------|-------------|------------|----------------------|
| 20   | D-limonene     | Terpene         | *Citrus aurantium*    | C_{10}H_{16}      | 136.23           | Colon cancer | In vitro | Inactivation of Akt pathway [104] |
|      |                |                 |                       |                  |                  | Lung cancer  | In vitro | Upregulation of Atg5 [105] |
|      |                |                 |                       |                  |                  | Prostate cancer | In vitro | Generation of ROS, and activation of caspase-3 and -9 [106] |
| 21   | Emodin         | Resin           | *Rheum palmatum*      | C_{15}H_{10}O_{5} | 270.24           | Breast cancer | In vitro | Activation of AhR-CYP1A1 signaling pathway [107] |
|      |                |                 |                       |                  |                  | Lung cancer  | In vitro | Suppression of HAS2-HA-CD44/RHAMM pathway [108] |
|      |                |                 |                       |                  |                  | Pancreatic cancer | In vitro, in vivo | Downregulation of NF-κB, VEGF, MMP-2, and -9 [109] |
|      |                |                 |                       |                  |                  | Colon cancer | In vitro | Suppression of PI3K/AKT signaling [110] |
|      |                |                 |                       |                  |                  | Prostate cancer | In vitro | Downregulation of VEGF [111] |
|      |                |                 |                       |                  |                  | Breast cancer | In vitro, in vivo | Suppression of Notch1, MMP-2, and -9 signaling [112] |
|      |                |                 |                       |                  |                  | Lung cancer  | In vitro | Activation of AMPK signaling pathway [113] |
|      |                |                 |                       |                  |                  | Ovarian cancer | In vitro | Induce DNA damage [114] |
|      |                |                 |                       |                  |                  | Prostate cancer | In vitro, in vivo | Inhibition of HSP90 function [115] |
|      |                |                 |                       |                  |                  | Head & neck cancer | In vitro, in vivo | Inhibition of beta-catenin expression [116] |
|      |                |                 |                       |                  |                  | Colon cancer | In vitro | Induction of ER stress through PERK/p-eIF2α/ATF4 and IRE1a pathways activation [117] |
| 22   | Epigallocatechin gallate (EGCG) | Catechin | *Camellia sinensis* | C_{22}H_{16}O_{11} | 458.4           | Breast cancer | In vitro | Activation of PI3K/Akt pathway [118] |
|      |                |                 |                       |                  |                  | Lung cancer  | In vitro, in vivo | Induction of Ca2+/CaM-dependent ferroptosis [119] |
|      |                |                 |                       |                  |                  | Liver cancer  | In vitro, in vivo | Induction of oxidative stress-mediated mitochondrial apoptosis [73] |
|      |                |                 |                       |                  |                  | Oral cancer  | In vitro | Regulation of MAPK pathway [120] |
|      |                |                 |                       |                  |                  | Bladder cancer | In vitro, in vivo | Increase in p-JNK level and induce c-Jun and Bcl-2 phosphorylation [121] |
|      |                |                 |                       |                  |                  | Bone cancer  | In vitro, in vivo | Activation of ROS/JNK signaling [122] |
|      |                |                 |                       |                  |                  | Colon cancer | In vitro | Activation of JNK pathway [123] |
|      |                |                 |                       |                  |                  | Cervical cancer | In vitro | Regulation of ERK1/2 signaling [124] |
| Sr # | Phytochemicals       | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type         | Study Type          | Targets and Mechanisms                                                                 |
|-----|----------------------|-----------------|-----------------------|--------------------|-------------------|---------------------|---------------------|----------------------------------------------------------------------------------------|
| 24  | Evodiamine           | Alkaloid         | *Evodia rutaecarpa*   | **C_{19}H_{27}N_{3}O** | 303.4             | Lung cancer         | In vitro, in vivo   | Elevation of CD8+ T cells and downregulation of MUC1-C/PD-L1 axis [125]                 |
|     |                      |                 |                       |                    |                   | Thyroid cancer      | In vitro            | Through M phase cell cycle arrest and apoptosis’s induction [126]                      |
|     |                      |                 |                       |                    |                   | Prostate cancer     | In vitro            | Activation of caspase-3 and -9 [127]                                                   |
|     |                      |                 |                       |                    |                   | Liver cancer        | In vitro            | Deactivation of PI3K/ AKT pathway [128]                                                |
|     |                      |                 |                       |                    |                   | Bladder cancer      | In vitro            | Enhance activation of P38 and [NK signaling [129]                                     |
|     |                      |                 |                       |                    |                   | Colon cancer        | In vitro, in vivo   | Inhibition of acetyl-NF-kB, p65 and MMP-9 expression [130]                             |
|     |                      |                 |                       |                    |                   | Ovarian cancer      | In vitro            | Elevation of p27 and p21, and inhibition of Cdc2 expression [131]                       |
|     |                      |                 |                       |                    |                   | Pancreatic cancer   | In vitro            | Inhibition of NF-kB, p65, and Bcl-2 expression, while activate Bax and cleaved caspase-3 [132] |
| 25  | Flavopiridol         | Flavonoids       | *Dysoxylum binecariferum* | **C_{21}H_{20}ClNO_{5}** | 41.8              | Breast cancer       | In vitro            | Inhibition of cyclin-dependent kinases [133]                                           |
|     |                      |                 |                       |                    |                   | Thyroid cancer      | In vitro, in vivo   | Reduction in Cyclin-dependent kinases (CDK) and MCL1 levels [134]                     |
|     |                      |                 |                       |                    |                   | Bile duct cancer    | In vitro, in vivo   | Suppression of cyclin-dependent kinase pathway [135]                                  |
|     |                      |                 |                       |                    |                   | Head & neck cancer  | In vitro, in vivo   | Reduction in cyclin D1 expression [136]                                                |
|     |                      |                 |                       |                    |                   | Lung cancer         | In vitro            | Reduction in E-cadherin level [137]                                                   |
|     |                      |                 |                       |                    |                   | Esophageal cancer   | In vitro, in vivo   | Decrease in c-Myc expression [138]                                                     |
| 26  | Gallic Acid          | Phenolic acid    | *Galanthus nivalis*   | **C_{7}H_{4}O_{5}** | 170.12            | Lung cancer         | In vitro, in vivo   | Inhibition of PI3K/Akt pathway [139]                                                   |
|     |                      |                 |                       |                    |                   | Liver cancer        | In vitro            | Suppression of Wnt/β-catenin signaling [140]                                           |
|     |                      |                 |                       |                    |                   | Breast cancer       | In vitro, in vivo   | Increases expression of cleaved caspase-7, -9, and p53, while reduces expression of Bcl-2, and PARP [141] |
|     |                      |                 |                       |                    |                   | Colon cancer        | In vitro, in vivo   | Inhibition of SRC and EGFR phosphorylation [142]                                       |
|     |                      |                 |                       |                    |                   | Gastric cancer      | In vitro            | Increases expression of caspase-3, -8, and P53 gene [143]                              |
|     |                      |                 |                       |                    |                   | Prostate cancer     | In vitro            | Generation of ROS [144]                                                               |
|     |                      |                 |                       |                    |                   | Ovarian cancer      | In vitro, in vivo   | Inhibition of carbonic anhydrase IX protein [145]                                      |
|     |                      |                 |                       |                    |                   | Pancreatic cancer   | In vitro            | Downregulation of protein Bcl-.2 while increases in BAX expression [146]              |
### Table 2. Cont.

| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|-----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|------------------------|
| 27   | Gambogic acid   | Resin           | *Carcinia hanburyi*   | C_{38}H_{44}O_{8}  | 628.7           | Lung cancer | In vitro, in vivo | Downregulation of Bcl-2, and upregulation of Bax expression [147] |
|      |                 |                 |                       |                    |                  | Breast cancer| In vitro, in vivo | Increase the expression of Fas, cleaved caspase-3, -8, -9 and Bax proteins [146] |
|      |                 |                 |                       |                    |                  | Liver cancer | In vitro       | Induces apoptosis through caspases 3, -7, -8 and -9 [149] |
|      |                 |                 |                       |                    |                  | Prostate cancer| In vitro       | Induction of ROS production [150] |
|      |                 |                 |                       |                    |                  | Colon cancer | In vitro, in vivo | Inhibition of Akt-mTOR signaling [151] |
|      |                 |                 |                       |                    |                  | Gastric cancer | In vitro, in vivo | Downregulation of circ_ASAP2 and CDK7, while upregulation of miR-33a-5p expression [152] |
| 28   | Genistein       | Isoflavones     | *Glycine max*         | C_{15}H_{10}O_{5}  | 270.24          | Liver cancer | In vitro       | Upregulation of Bax, cleaved caspase-3 and -9 and downregulation of Bcl-2 expression [153] |
|      |                 |                 |                       |                    |                  | Colon cancer | In vitro, in vivo | Suppression of MiR-95, Akt and SGK1 signaling [154] |
|      |                 |                 |                       |                    |                  | Prostate cancer| In vitro, in vivo | Decrease MMP-2 expression [155] |
|      |                 |                 |                       |                    |                  | Lung cancer  | In vitro       | Downregulation of FoxM1 [156] |
| 29   | Gingerol        | Phenol          | *Zingiber officinale* | C_{17}H_{26}O_{4}  | 294.4           | Breast cancer| In vitro       | Induction of p53-dependent intrinsic apoptosis [157] |
|      |                 |                 |                       |                    |                  | Oral cancer  | In vitro       | Activate caspases and increase Apaf-1 expression [158] |
|      |                 |                 |                       |                    |                  | Cervical cancer | In vitro     | Reduction in ROS and iron accumulation and suppression of USP14 expression [159] |
|      |                 |                 |                       |                    |                  | Lung cancer  | In vitro, in vivo | Inhibition of PI3K/AKT signaling [160] |
|      |                 |                 |                       |                    |                  | Pancreatic cancer | In vitro     | Breast cancer | Downregulation of estrogen receptor [161] |
|      |                 |                 |                       |                    |                  | Lung cancer  | In vitro, in vivo | Inhibition of p62/SQSTM1 signaling [162] |
|      |                 |                 |                       |                    |                  | Prostate cancer| In vitro, in vivo | Suppression of STAT3 expression [163] |
|      |                 |                 |                       |                    |                  | Bone cancer  | In vitro       | Inhibition of STAT3 and activation of caspase-3/9 [164] |
|      |                 |                 |                       |                    |                  | Ovarian cancer| In vitro       | Induction of apoptosis by activation of caspase-3 [165] |
|      |                 |                 |                       |                    |                  | Kidney cancer | In vitro       | Suppression of JAK2-STAT3 pathway [166] |
| 30   | Ginkgetin       | Flavonoid       | *Ginkgo biloba*       | C_{32}H_{22}O_{10} | 566.5           | Breast cancer| In vitro, in vivo | Induces ROS-mediated apoptosis [167] |
|      |                 |                 |                       |                    |                  | Gastric cancer| In vitro       | Downregulation of PI3K/AKT pathway [168] |
|      |                 |                 |                       |                    |                  | Prostate cancer| In vitro       | Induces DNA damage [169] |
|      |                 |                 |                       |                    |                  | Ovarian cancer| In vitro       | Upregulation of Fas and FasL expression [170] |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type       | Study Type | Targets and Mechanisms                                                                 |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------------|------------|----------------------------------------------------------------------------------------|
| 32   | Gossypol       | Phenol          | Gossypium hirsutum    | C_{30}H_{30}O_{8}   | 518.6            | Colon cancer      | In vitro   | Suppression of genes coding expression for CLAUDIN1, FAS, IL2, and IL8 [171]            |
|      |                |                 |                       |                    |                  | Breast cancer     | In vitro   | Suppression of IKBKE, CCL2 and MAPK1 expression [172]                                   |
|      |                |                 |                       |                    |                  | Lung cancer       | In vitro   | Decrease EGFR phosphorylation and AKT/ERK signaling [173]                                |
|      |                |                 |                       |                    |                  | Prostate cancer   | In vitro   | Activation of p53 protein [174]                                                          |
|      |                |                 |                       |                    |                  | Ovarian cancer    | In vitro   | Cause changes in thiol/redox states of proteins associated with glycolysis and stress responses [175] |
|      |                |                 |                       |                    |                  | Cervical cancer   | In vitro, in vivo| Inhibition of FAK signaling and reversing TGF-β1-induced EMT [176]                      |
|      |                |                 |                       |                    |                  | Head & neck cancer| In vivo   | Inhibition of Bcl-X<sub>L</sub> expression [177]                                        |
|      |                |                 |                       |                    |                  | Skin cancer       | In vitro   | Induces mitochondria-dependent apoptosis [178]                                          |
| 33   | Harmine        | Alkaloid         | Peganum harmala       | C_{13}H_{12}N_{2}O  | 212.25           | Breast cancer     | In vitro, in vivo| Downregulation of TAZ [179]                                                             |
|      |                |                 |                       |                    |                  | Thyroid cancer    | In vitro, in vivo| Downregulation of Bcl-2 and upregulation of Bax expression [180]                       |
|      |                |                 |                       |                    |                  | Gastric cancer    | In vitro   | Inhibition of Akt/mTOR/p70S6K signaling [181]                                           |
|      |                |                 |                       |                    |                  | Pancreatic cancer | In vitro   | Suppression of AKT/mTOR pathway [182]                                                   |
|      |                |                 |                       |                    |                  | Ovarian cancer    | In vitro   | Inhibition of ERK/CREB pathway [183]                                                    |
|      |                |                 |                       |                    |                  | Lung cancer       | In vitro   | Suppression of AKT phosphorylation and enhances ROS generation [184]                   |
| 34   | Hesperidin     | Flavonoid        | Citrus lemon          | C_{28}H_{34}O_{15}  | 610.6            | Lung cancer       | In vitro   | Downregulation of FGF and NF-κB signal transduction pathways [185]                      |
|      |                |                 |                       |                    |                  | Gastric cancer    | In vitro   | Increase in ROS levels and regulation of MAPK signaling [135]                           |
|      |                |                 |                       |                    |                  | Liver cancer      | In vitro   | Downregulation of Bcl-xL and upregulation of Bax, Bak, and tBid proteins [186]         |
|      |                |                 |                       |                    |                  | Skin cancer       | In vitro   | Induces DNA damage [187]                                                                |
|      |                |                 |                       |                    |                  | Prostate cancer   | In vitro   | Induces apoptosis triggered by ROS generation [188]                                    |
|      |                |                 |                       |                    |                  | Breast cancer     | In vitro   | Inhibition of PD-L1 expression via downregulation of Akt and NF-κB signaling [189]     |
| Sr # | Phytochemicals  | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type   | Study Type       | Targets and Mechanisms |
|------|-----------------|-----------------|-----------------------|-------------------|------------------|---------------|-----------------|-----------------------|
| 35   | Hispidulin      | Flavone         | *Salvia involucrate*  | C_{16}H_{12}O_{6}  | 300.26           | Lung cancer   | In vitro, in vivo | Induces ROS-mediated apoptosis via ER stress pathway [190] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro, in vivo | Upregulation of PPARγ signaling [191] |
|      |                 |                 |                       |                   |                  | Kidney cancer | In vitro, in vivo | Activation of ROS/JNK signaling [192] |
|      |                 |                 |                       |                   |                  | Gastric cancer| In vitro         | Activate ERK1/2 and NAG-1 signaling [193] |
|      |                 |                 |                       |                   |                  | Breast cancer | In vitro         | Increase expression of H2AX, caspase-3, and -9 [194] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Activation of AMPK signaling [195] |
|      |                 |                 |                       |                   |                  | Kidney cancer | In vitro         | Downregulation of AKT and FAK pathways [196] |
|      |                 |                 |                       |                   |                  | Cervical cancer| In vitro         | Disruption of mitochondrial membrane potential and intracellular free Ca2+ concentration [197] |
|      |                 |                 |                       |                   |                  | Pancreatic cancer| In vitro         | Inhibition of TGM2 expression [198] |
|      |                 |                 |                       |                   |                  | Colon cancer  | In vitro         | Activation of ATM and p53-Bax axis [199] |
| 36   | Kaempferol      | Flavonoid       | *Spinacia oleracea*   | C_{15}H_{10}O_{6}  | 286.24           | Lung cancer   | In vitro, in vivo | Suppression of caspase-7 and -12, and AKT pathway [200] |
|      |                 |                 |                       |                   |                  | Breast cancer | In vitro         | Inhibition of NF-κB activation [201] |
|      |                 |                 |                       |                   |                  | Gastric cancer| In vitro         | Inhibition of STAT3 signaling [202] |
|      |                 |                 |                       |                   |                  | Colon cancer  | In vitro         | Downregulation of PI3K/akt/GSK3β signaling [203] |
|      |                 |                 |                       |                   |                  | Lung cancer   | In vitro         | Downregulation of Cyclin E1 expression [204] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Upregulation of Bax, F53, and downregulation of Bel-2 expressions [205] |
| 37   | Kurarinone      | Flavonoid       | *Sophora flavescens*  | C_{26}H_{30}O_{6}  | 438.5            | Lung cancer   | In vitro, in vivo | Inhibition of PI3/K/Akt/mTOR pathway [206] |
|      |                 |                 |                       |                   |                  | Breast cancer | In vitro         | Downregulation of PI3K/AKT/GSK3β signaling [203] |
|      |                 |                 |                       |                   |                  | Colon cancer  | In vitro         | Downregulation of Cyclin E1 expression [204] |
|      |                 |                 |                       |                   |                  | Lung cancer   | In vitro         | Upregulation of Bax, F53, and downregulation of Bel-2 expressions [205] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Inhibition of PI3/K/Akt/mTOR pathway [206] |
| 38   | Lappaconitine   | Diterpenoid     | *Aconitum sinomontanum* | C_{32}H_{44}N_{2}O_{8} | 584.7           | Lung cancer   | In vitro         | Inhibition of PI3/K/Akt/mTOR pathway [206] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Downregulation of PI3K/AKT/GSK3β signaling [203] |
|      |                 |                 |                       |                   |                  | Colon cancer  | In vitro         | Downregulation of Cyclin E1 expression [204] |
|      | Licochalcone A  | Chalcone        | *Glycyrrhiza glabra*  | C_{21}H_{22}O_{4}  | 338.4            | Breast cancer | In vitro         | Inhibition of PI3K/Akt/mTOR pathway [206] |
|      |                 |                 |                       |                   |                  | Bladder cancer| In vitro         | Induces ER stress-dependent apoptosis caused by activation of ER-specific caspase-12 [207] |
|      |                 |                 |                       |                   |                  | Lung cancer   | In vitro         | Induces ERK and p38 activation while suppresses JNK signaling [208] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Downregulation of MKK4/JNK [209] |
| 40   | Liriodenine     | Alkaloid        | *Enicosanthellum pulcherum* | C_{17}H_{20}NO_{4} | 275.26           | Breast cancer | In vitro         | Upregulation of p53 [210] |
|      |                 |                 |                       |                   |                  | Lung cancer   | In vitro         | Upregulation of p53 [210] |
|      |                 |                 |                       |                   |                  | Liver cancer  | In vitro         | Upregulation of CAOV-3 cell cycle in S phase [212] |
|      |                 |                 |                       |                   |                  | Ovarian cancer| In vitro         | Inhibition of progression of CAOV-3 cell cycle in S phase [212] |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|-------------------|-----------------|-------------|------------|-----------------------|
| 41   | Luteolin       | Flavonoid       | Reseda luteola         | C_{15}H_{10}O_{6}  | 286.24          | Liver cancer | In vitro  | Increases caspase-8 and decreases Bcl-2 expression [213] |
|      |                |                 |                       |                   |                 | Colon cancer | In vitro  | Uptregulation of Nrf2 expression [214] |
|      |                |                 |                       |                   |                 | Gastric cancer | In vitro  | Inhibition of STAT3 phosphorylation [215] |
|      |                |                 |                       |                   |                 | Oral cancer  | In vitro  | Suppression of EMT-induced transcription factors [216] |
|      |                |                 |                       |                   |                 | Breast cancer | In vitro  | Suppression of NF-κB/c-Myc activation and hTERT transcription [217] |
|      |                |                 |                       |                   |                 | Pancreatic cancer | In vitro  | Inhibition of VEGF expression [218] |
|      |                |                 |                       |                   |                 | Lung cancer  | In vitro  | Inhibition of FAK-Src signaling [219] |

| 42   | Lycopene       | Carotenoid      | Solanum lycopersicum  | C_{40}H_{56}      | 536.9           | Breast cancer | In vitro  | Inhibition of Akt phosphorylation [220] |
|      |                |                 |                       |                   |                 | Prostate cancer | In vitro, in vivo | Downregulation of IL1, IL6, IL8, and TNF-α levels [221] |
|      |                |                 |                       |                   |                 | Colon cancer  | In vitro  | Suppression of NF-κB and JNK signaling [222] |
|      |                |                 |                       |                   |                 | Pancreatic cancer | In vitro  | Inhibition of ROS-Mediated NF-κB Signaling [223] |
|      |                |                 |                       |                   |                 | Lung cancer  | In vitro, in vivo | Induction of RARβ expression [224] |
|      |                |                 |                       |                   |                 | Gastric cancer | In vivo  | Increase in SOD, and CAT, while decrease in MDA levels [225] |
|      |                |                 |                       |                   |                 | Cervical cancer | In vitro  | Upregulation of Bax, and downregulation of Bcl-2 expression [226] |
|      |                |                 |                       |                   |                 | Skin cancer  | In vivo  | Inhibition of PCNA expression [227] |
|      |                |                 |                       |                   |                 | Brain cancer  | In vitro  | Activation of caspase-3 pathway [228] |
|      |                |                 |                       |                   |                 | Ovarian cancer | In vitro, in vivo | Decrease in integrin α5 expression and MAPK activation [229] |

| 43   | Lycorine       | Alkaloid        | Crinum asiaticum      | C_{18}H_{17}NO_{4} | 287.31          | Breast cancer | In vitro, in vivo | Inhibition of STAT3 signalin path [230] |
|      |                |                 |                       |                   |                 | Gastric cancer | In vitro, in vivo | Enhances FBXW7-MCL1 axis level [224] |
|      |                |                 |                       |                   |                 | Prostate cancer | In vitro, in vivo | Inhibition of JAK/STAT signaling [231] |
|      |                |                 |                       |                   |                 | Lung cancer  | In vitro, in vivo | Inhibition of Wnt/β-catenin signaling [232] |
|      |                |                 |                       |                   |                 | Liver cancer  | In vitro  | Inhibition of ROCK1/cofilin-induced actin dynamics [233] |

| 44   | Magnolol       | Lignan          | Magnolia officinalis  | C_{18}H_{18}O_{2}  | 266.3           | Lung cancer  | In vitro, in vivo | Downregulation of Akt/ mTOR pathway [234] |
|      |                |                 |                       |                   |                 | Gallbladder cancer | In vitro, in vivo | Increase in p53 expression [235] |
|      |                |                 |                       |                   |                 | Liver cancer  | In vitro  | Inhibition of ERK-modulated metastatic process [236] |
|      |                |                 |                       |                   |                 | Prostate cancer | In vitro  | Downregulation of MMP-2 and MMP-9 expression [237] |
|      |                |                 |                       |                   |                 | Esophageal cancer | In vitro  | Activation of MAPK pathway [238] |
| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|----------------------|
| 45   | Matrine        | Alkaloid        | *Sophora flavescens*  | C_{15}H_{24}N_{2}O | 248.36           | Prostate cancer | In vitro   | Enhances expression of GADD45B, tumor suppressor gene or AKT/GSK3β/β-catenin [239] |
|      |                |                 |                       |                    |                  | Ovarian cancer  | In vitro, in vivo | Suppression of PI3K/AKT/mTOR pathway expression [240] |
|      |                |                 |                       |                    |                  | Colon cancer   | In vitro   | Upregulation of Bax, downregulation of Bcl-2, and activation of caspase-3 and -9 [241] |
|      |                |                 |                       |                    |                  | Liver cancer   | In vitro, in vivo | Upregulation of miR-345-5p and downregulation of circ_0027345 and HOXD3 [242] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro   | Downregulation of C-C chemokine receptor type 7 (CCR7) [243] |
| 46   | Myricetin      | Flavonoid       | *Myrica nagi Thunb*   | C_{15}H_{10}O_{8}  | 318.23           | Thyroid cancer | In vitro   | DNA damaging and inducing the release of apoptosis-inducing factor (AIF) [244] |
|      |                |                 |                       |                    |                  | Bladder cancer | In vitro, in vivo | Activation of caspase-3, and inhibition of Akt and MMP-9 expression [245] |
|      |                |                 |                       |                    |                  | Colon cancer   | In vitro   | Increases BAX/BCL2 ratio and AIF release [246] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro   | Inhibition of PIM1 and disruption of PIM1/CXCR4 interaction [247] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro   | Enhances intracellular ROS production [248] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro   | Inhibition of FAK-ERK signaling pathway [249] |
| 47   | Nimbolide      | Limonoid triterpene | *Azadirachta indica* | C_{27}H_{30}O_{7} | 466.5            | Pancreatic cancer | In vitro, in vivo | Reduction in PI3K/AKT/mTOR and ERK signaling [250] |
|      |                |                 |                       |                    |                  | Colon cancer   | In vitro, in vivo | Inhibition of Bcl-x, CXCR4, VEGF, and NF-κB [251] |
|      |                |                 |                       |                    |                  | Bladder cancer | In vitro   | Stimulation of p38 MAPK and AKT phosphorylation [252] |
| 48   | Noscapine      | Alkaloid        | *Papaver somniferum*  | C_{22}H_{32}NO_{7} | 413.4            | Colon cancer   | In vitro   | Inhibition of PI3K/AKT/mTOR pathway [253] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro   | Decreases NF-κB and increases IκBα expression [254] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro, in vivo | Upregulation of PARP, Bax, and repression of Bcl2 expression [255] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vivo    | Suppression of microtubule dynamics [256] |
| 49   | Oridonin       | Diterpenoid     | *Rhabdosia rubescens* | C_{20}H_{26}O_{6}  | 364.4            | Colon cancer   | In vitro, in vivo | Downregulation of GLUT1 and induction of autophagy [257] |
|      |                |                 |                       |                    |                  | Liver cancer   | In vitro, in vivo | Inhibition of Akt pathway [258] |
|      |                |                 |                       |                    |                  | Ovarian cancer  | In vitro   | Suppression of mTOR pathway [259] |
|      |                |                 |                       |                    |                  | Bladder cancer  | In vitro, in vivo | Inactivation of ERK and AKT signaling pathways [260] |
|      |                |                 |                       |                    |                  | Esophageal cancer | In vitro, in vivo | Suppression of AKT signaling [261] |
| Sr # | Phytochemicals | Chemical Nature | Plant’s Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type       | Study Type          | Targets and Mechanisms                                                                 |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------------|-------------------|----------------------------------------------------------------------------------------|
| 50   | Oxymatrine     | Alkaloid         | *Sophora flavescens*  | C_{13}H_{22}N_{2}O_{2} | 264.36           | Breast cancer     | In vitro          | Decrease in expression of MMPs and regulation of Integrin β1/FAK pathway [262]          |
|      |                |                  |                       |                    |                  | Bone cancer       | In vitro, in vivo | Activation of PPAR-γ and inhibition of Nrf2 pathways [263]                               |
|      |                |                  |                       |                    |                  | Cervical cancer   | In vitro          | Suppression of AKT/mTOR [264]                                                           |
|      |                |                  |                       |                    |                  | Breast cancer     | In vitro          | Suppress the PI3K/Akt [265]                                                            |
|      |                |                  |                       |                    |                  | Pancreatic cancer | In vitro          | Downregulation of Livin and Survivin expression and upregulation of Bax/Bcl-2 ratio [266] |
|      |                |                  |                       |                    |                  | Prostate cancer   | In vitro, in vivo | Increase in expression of p53 and Bax, and decrease in Bcl-2 level [267]               |
| 51   | Physapubescin B| Steroid          | *Physalis pubescens*  | C_{30}H_{42}O_{8}   | 530.6            | Ovarian cancer    | In vitro          | Suppress transcriptional activity of STAT3 [268]                                       |
|      |                |                  |                       |                    |                  | Kidney cancer     | In vitro, in vivo | Decreases expression of HIF-2α and activation of caspase-3 and -8 [269]                |
| 52   | Pinostrobin    | Flavonoid        | *Boesenbergia rotunda*| C_{16}H_{14}O_{4}  | 270.28           | Cervical cancer   | In vitro          | Increases expressions of TRAIL, FADD and production of ROS [270]                      |
|      |                |                  |                       |                    |                  | Breast cancer     | In vitro          | Downregulation of FAK and RhoA signaling [271]                                         |
|      |                |                  |                       |                    |                  | Lung cancer       | In vitro          | Via promoting apoptosis [272]                                                          |
|      |                |                  |                       |                    |                  | Prostate cancer   | In vitro          | Decrease in cyclins B expression [273]                                                 |
| 53   | Piperine       | Alkaloid          | *Piper nigrum*        | C_{17}H_{19}NO_{3} | 285.34           | Colon cancer      | In vitro          | Suppression of Wnt/β-catenin pathway [274]                                             |
|      |                |                  |                       |                    |                  | Lung cancer       | In vitro          | Induces p53-mediated cell cycle arrest and apoptosis via activation of caspase-3 and -9 cascades [275] |
|      |                |                  |                       |                    |                  | Breast cancer     | In vitro, in vivo | Induction of cell apoptosis and cell cycle blockage [276]                              |
|      |                |                  |                       |                    |                  | Prostate cancer   | In vitro          | Downregulation of cyclin A & D1 [277]                                                  |
| 54   | Piperlongumine | Alkaloid          | *Piper longum*        | C_{17}H_{19}NO_{5} | 317.34           | Lung cancer       | In vitro          | Inhibition of Akt phosphorylation [278]                                                |
|      |                |                  |                       |                    |                  | Prostate cancer   | In vitro          | Induces DNA damage [279]                                                               |
|      |                |                  |                       |                    |                  | Colon cancer      | In vitro          | Induces DNA damage via increasing ROS production [280]                                 |
| 55   | Plumbagin      | Alkaloid          | *Plumbago saginata*   | C_{11}H_{22}O_{3}  | 188.18           | Breast cancer     | In vitro          | Upregulation of p53 and p21 [281]                                                      |
|      |                |                  |                       |                    |                  | Colon cancer      | In vitro          | Induction of ROS formation [282]                                                       |
|      |                |                  |                       |                    |                  | Liver cancer      | In vitro, in vivo | Downregulation of SIVA/mTOR signaling [283]                                            |
|      |                |                  |                       |                    |                  | Prostate cancer   | In vitro, in vivo | Induction of ROS production, and activation of ER stress [284]                        |
|      |                |                  |                       |                    |                  | Lung cancer       | In vitro          | Activation of caspase-9 and ROS production [285]                                      |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type     | Study Type | Targets and Mechanisms                                                                                                                                 |
|-----|----------------|----------------|----------------------|-------------------|------------------|----------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 56  | Pristimerin    | Triterpenoid    | Mortonia greggii     | C_{30}H_{46}O_{4} | 464.6            | Esophageal cancer | In vitro, in vivo | Inhibition of STAT3-PLK1-AKT signaling [286]                                                                                                             |
|     |                |                |                      |                   |                  | Bone cancer     | In vitro     | Downregulation of c-Myc expression [287]                                                                                                               |
|     |                |                |                      |                   |                  | Cervical cancer | In vitro     | Downregulation of MMP 2, 9, β-catenin and N-cadherin, while upregulation of E-cadherin signaling [288]                                                   |
|     |                |                |                      |                   |                  | Colon cancer    | In vitro     | Decreases in AKT expression [289]                                                                                                                        |
|     |                |                |                      |                   |                  | Oral cancer     | In vitro     | Inhibition of MAPK/Erk1/2 and Akt signaling [290]                                                                                                         |
|     |                |                |                      |                   |                  | Prostate cancer | In vitro     | Inhibition of HIF-1α [291]                                                                                                                               |
|     |                |                |                      |                   |                  | Lung cancer     | In vitro     | Downregulation of integrin β1 and MMP2 expression [292]                                                                                                 |
|     |                |                |                      |                   |                  | Pancreatic cancer | In vitro     | Inhibition of Akt/NF-κB/mTOR signaling [293]                                                                                                           |
|     | Pterostilbene  | Stilbenoid     | Polygonum cuspidatum | C_{16}H_{16}O_{3} | 256.3            | Ovarian cancer  | In vitro     | Decreases release of NF-κB p50, and NF-κB p65 [294]                                                                                                       |
|     |                |                |                      |                   |                  | Lung cancer     | In vitro, in vivo | Enhance ROS generation, caspase-3 activity and ER stress [295]                                                                                           |
|     |                |                |                      |                   |                  | Breast cancer   | In vitro     | Inactivate Akt and mTOR signaling pathways [296]                                                                                                          |
|     |                |                |                      |                   |                  | Colon cancer    | In vitro, in vivo | Facilitate DNA repairing mediated through Top1/Tdp1 pathway [297]                                                                                       |
|     | Puerarin       | Isoflavone     | Pueraria radix       | C_{21}H_{20}O_{9} | 416.4            | Colon cancer    | In vitro     | Increase Bax expression and caspase-3 activation [298]                                                                                                   |
|     |                |                |                      |                   |                  | Prostate cancer | In vitro     | Inhibition of Keap1/Nrf2/ARE signaling pathways [299]                                                                                                      |
|     |                |                |                      |                   |                  | Lung cancer     | In vitro, in vivo | Inhibition of PI3K/Akt pathway [300]                                                                                                                       |
|     |                |                |                      |                   |                  | Liver cancer    | In vitro     | Modulation of MAPK signaling pathway [301]                                                                                                               |
|     |                |                |                      |                   |                  | Brain cancer    | In vitro     | Suppression of p-Akt and Bcl-2, while enhancement of Bax and cleaved caspase-3 expression [302]                                                        |
|     | Quercetin      | Flavonoid      | Allium cepa          | C_{15}H_{10}O_{7} | 302.23           | Thyroid cancer  | In vitro     | Upregulation of Pro-NAG-1/GDF15 [303]                                                                                                                    |
|     |                |                |                      |                   |                  | Breast cancer   | In vitro     | Inactivation of caspase-3 pathway [304]                                                                                                                   |
|     |                |                |                      |                   |                  | Liver cancer    | In vitro     | Inhibition of PI3K/Akt and ERK pathways [305]                                                                                                           |
|     |                |                |                      |                   |                  | Prostate cancer | In vitro     | Enhances release of tumor suppressor genes i.e., PTEN, p53 and TSC [306]                                                                               |
|     |                |                |                      |                   |                  | Lung cancer     | In vitro     | Inhibition of NF-κB Signaling [307]                                                                                                                        |
|     | Resveratrol    | Stilbenoid     | Polygonum cuspidatum | C_{14}H_{12}O_{3} | 228.24           | Colon cancer    | In vitro     | Inactivates PI3K/Akt signaling [308]                                                                                                                      |
|     |                |                |                      |                   |                  | Breast cancer   | In vitro     | Suppression of Integrin av/β3 expression [309]                                                                                                           |
|     |                |                |                      |                   |                  | Ovarian cancer  | In vitro     | Inactivation of STAT3 signaling [310]                                                                                                                      |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|------------------------|
| 61   | Rutin          | Flavonoid       | *Ruta graveolens*     | C_{27}H_{30}O_{16} | 610.5            | Pancreatic cancer | In vitro | Suppression of NAF-1 expression, induces ROS accumulation, and activation of Nrf2 signaling [311] |
|      |                |                 |                       |                    |                  | Gastric cancer  | In vitro | Upregulation of Bax, cleaved caspase-3 and -8 while suppression of NF-κB activation [312] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro, in vivo | Decreases SIRT1-mediated NF-κB activation [313] |
|      |                |                 |                       |                    |                  | Skin cancer    | In vitro, in vivo | Deacetylation of SIRT1-activated NF-κB [314] |
| 62   | Safranal       | Alkaloid        | *Crocus sativus*      | C_{10}H_{14}O     | 150.22           | Colon cancer  | In vitro | Inhibition of caspase-3 expression [315] |
|      |                |                 |                       |                    |                  | Brain cancer   | In vitro | Upregulation of P53 expression [265] |
|      |                |                 |                       |                    |                  | Skin cancer    | In vitro | Suppression of PI3K/Akt and Wnt/β-catenin signaling [316] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro, in vivo | Inhibition of tyrosine kinase c-Met receptor [317] |
| 63   | Shikonin       | Quinone         | *Lithospermum erythrorhizon* | C_{16}H_{16}O_{5} | 288.29           | Lung cancer    | In vitro | Downregulation of PFKFB2 expression [322] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro | Reduction in peroxiredoxin V (PrxV) expression [323] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro, in vivo | Induces necroptosis by decreasing caspase-8 and increasing pRIP1 and pRIP3 [324] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro | Inhibition of DNA and RNA synthesis [321] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro | Downregulation of PKM2 expression [325] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro | Decreases Bcl-2 expression and increases BAX, caspase-3 and -9 expression [326] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro | Inhibition of PKM2 expression [325] |
|      |                |                 |                       |                    |                  | Ovarian cancer | In vitro | Decreases MAPK pathway-mediated induction of apoptosis [327] |
|      |                |                 |                       |                    |                  | Skin cancer    | In vitro, in vivo | Inhibition of MAPK pathway-mediated induction of apoptosis [327] |
|      |                |                 |                       |                    |                  | Bile duct cancer | In vitro | Inhibition of epidermal growth factor receptor signaling [329] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro | Inhibition Akt and STAT signaling pathway [330] |
|      |                |                 |                       |                    |                  | Lung cancer    | In vitro, in vivo | Inhibition of STAT3 and NF-κB signaling [331] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro | Inhibits secretion of CCL2 [332] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro, in vivo | Inhibits apoptosis and G2/M cell cycle arrest [333] |
Table 2. Cont.

| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|------------------------|
| 65   | Silibinin      | Flavonolignan   | Silybum marianum      | C_{25}H_{22}O_{10} | 482.4            | Breast cancer | In vivo    | Inhibition of EGF–EGFR signaling pathway [334] |
|      |                |                 |                       |                    |                  | Lung cancer  | In vitro, in vivo | Activation of EGFR/LOX pathway [335] |
|      |                |                 |                       |                    |                  | Ovarian cancer | In vitro, in vivo | Inhibition of ERK and Akt pathway [336] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro   | Suppression of vimentin and MMP-2 expression [337] |
|      |                |                 |                       |                    |                  | Skin cancer   | In vivo    | Via Pro-Oxidant activity [338] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro   | Downregulation of COX-2, VEGF, MMP-2, & -9, and CXCR-4 expression [339] |
|      |                |                 |                       |                    |                  | Gastric cancer | In vitro   | Inhibition of STAT3 pathway [340] |
|      |                |                 |                       |                    |                  | Oral cancer   | In vitro, in vivo | Induction of DR5/caspase-8 apoptotic signaling [289] |
|      |                |                 |                       |                    |                  | Gastric cancer | In vitro   | Inhibition of p-ERK and activation of p-p38 and p-JNK pathways [341] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro   | Increases ATF3 transcription through activation of JNK and IkB-α [291] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro   | Inhibition of cyclins (A, B1, D, E) and cyclin-dependent kinase pathway [337] |
|      |                |                 |                       |                    |                  | Breast cancer  | In vitro, in vivo | Regulation of MAPK signaling pathway [342] |
|      |                |                 |                       |                    |                  | Liver cancer   | In vivo    | Reduction in ROS levels [343] |
| 66   | Silymarin      | Flavonolignan   | Silybum marianum      | C_{25}H_{22}O_{10} | 482.4            | Gastric cancer | In vitro, in vivo | Inhibition of Erk1/2 MAPK phosphorylation [344] |
|      |                |                 |                       |                    |                  | Skin cancer   | In vitro   | Downregulation of hILP/XIAP [345] |
|      |                |                 |                       |                    |                  | Bone cancer   | In vitro   | Suppression of notch pathway [346] |
|      |                |                 |                       |                    |                  | Liver cancer   | In vitro   | Induction of apoptosis [347] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro, in vivo | Suppression of MUC1 expression [348] |
| 67   | Solamargine    | Alkaloid         | Solanum nigrum L.     | C_{45}H_{73}NO_{15} | 868.1            | Gastric cancer | In vitro, in vivo | Inhibition of Erk1/2 MAPK phosphorylation [344] |
|      |                |                 |                       |                    |                  | Skin cancer   | In vitro   | Downregulation of hILP/XIAP [345] |
|      |                |                 |                       |                    |                  | Bone cancer   | In vitro   | Suppression of notch pathway [346] |
|      |                |                 |                       |                    |                  | Liver cancer   | In vitro   | Induction of apoptosis [347] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro, in vivo | Suppression of MUC1 expression [348] |
| 68   | Stachydrine    | Alkaloid         | Herba Leonuri         | C_{7}H_{13}NO_{2}  | 143.18           | Breast cancer  | In vitro   | Inhibition of Akt/ERK pathways [349] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro   | Inhibits CXCR3 and CXCR4 expressions [350] |
| 69   | Sugiol         | Diterpene       | Salvia prionitis      | C_{20}H_{26}O_{2}  | 300.4            | Ovarian cancer | In vitro   | Blockage of RAF/MEK/ERK signaling pathway [351] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro, in vivo | Inhibits STAT3 activity and increase ROS level [352] |
|      |                |                 |                       |                    |                  | Pancreatic cancer | In vitro   | Induces ROS-mediated alterations in MMP [353] |
|      |                |                 |                       |                    |                  | Uterine cancer | In vitro   | Increases Bax and decreases Bcl-2 expressions [354] |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|------------------------|
| 70   | Tanshinone     | Terpenoids      | *Salvia miltiorrhiza* | C_{18}H_{12}O_{3}   | 276.3            | Lung cancer | In vitro, in vivo | Suppression of IL-8 through NF-κB and AP-1 Pathways [355] |
|      |                |                 |                       |                    |                  | Gastric cancer | In vitro, in vivo | Downregulation of STAT3 pathway [356] |
|      |                |                 |                       |                    |                  | Breast cancer | In vitro     | Suppression of HIF-1α and VEGF [357] |
|      |                |                 |                       |                    |                  | Ovarian cancer | In vitro, in vivo | Downregulation of Bcl-2, VEGF, COX2 and upregulation of Bax expressions [358] |
|      |                |                 |                       |                    |                  | Bladder cancer | In vitro    | Activation of caspases 3 and -9 [359] |
|      |                |                 |                       |                    |                  | Cervical cancer | In vitro, in vivo | Decrease in Bcl-2, HPV 16 and E7 protein levels, while increase in Bax and caspase-3 expressions [360] |
| 71   | Tectochrysin   | Flavonoids      | *Alpinia oxyphylla*   | C_{16}H_{12}O_{4}   | 268.26           | Colon cancer | In vitro     | Inhibition of NF-κB signaling [361] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro     | Suppression of PI3K/AKT pathway [362] |
|      |                |                 |                       |                    |                  | Lung cancer   | In vitro     | Inhibition of STAT3 signaling [363] |
| 72   | Tetrandrine    | Alkaloid        | *Stephania tetrandra* | C_{38}H_{42}N_{2}O_{6} | 622.7           | Cervical cancer | In vitro, in vivo | Downregulation of MMP2 and MMP9 [364] |
|      |                |                 |                       |                    |                  | Breast cancer | In vivo       | Upregulation of Caspase-3, Bax, and downregulation of Bcl-2, Survivin, and PARP signaling [365] |
|      |                |                 |                       |                    |                  | Gastric cancer | In vitro, in vivo | Activation of caspase-3 and -9, and upregulation of apaf-1 [366] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro     | Inhibition of EMT transition [367] |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro     | Induction of DR4 and DR5 expression, and TRAIL-mediated apoptosis [368] |
|      |                |                 |                       |                    |                  | Bone cancer   | In vitro, in vivo | Inhibition of PTEN/Akt, MAPK/Erk and Wnt signaling pathways [369] |
| 73   | Thymol         | Phenol          | *Thymus vulgaris*     | C_{10}H_{14}O       | 150.22           | Lung cancer   | In vitro     | Enhances cytoplasmic membrane permeability and cell apoptosis [370] |
|      |                |                 |                       |                    |                  | Breast cancer | In vitro     | |
|      |                |                 |                       |                    |                  | Prostate cancer | In vitro     | Suppression of Wnt/β-Catenin pathway [371] |
|      |                |                 |                       |                    |                  | Colon cancer  | In vitro     | Activation of Bax, PARP, and caspase-8 proteins [372] |

Table 2. Cont.
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|----------------------|-------------------|------------------|-------------|------------|------------------------|
| 74   | Thymoquinone   | Quinone         | *Nigella sativa*     | C_{10}H_{12}O_{2} | 164.2            | Kidney cancer | In vitro  | Inhibition of AKT phosphorylation [373] |
|      |                |                 |                      |                   |                  | Breast cancer | In vitro, in vivo | Through phosphorylation of p38 via ROS generation [374] |
|      |                |                 |                      |                   |                  | Bladder cancer | In vitro  | Inhibition of mTOR signaling [375] |
|      |                |                 |                      |                   |                  | Colon cancer  | In vitro  | Inhibition of STAT3, JAK2- and EGF receptor tyrosine kinase [376] |
|      |                |                 |                      |                   |                  | Gastric cancer | In vitro, in vivo | Inhibition of STAT3 pathway [377] |
|      |                |                 |                      |                   |                  | Liver cancer   | In vitro  | Inhibition of IL-8 expression, and activation of TRAIL receptors [378] |
|      |                |                 |                      |                   |                  | Lung cancer    | In vitro  | Reduction in ERK1/2 phosphorylation [379] |
|      |                |                 |                      |                   |                  | Oral cancer    | In vitro  | Downregulation of p38β MAPK [380] |
|      |                |                 |                      |                   |                  | Pancreatic cancer | In vitro  | Downregulation of mucin 4 expression [381] |
| 75   | Ursolic acid   | Triterpenoids    | *Oldenlandia diffusa*| C_{30}H_{48}O_{3} | 456.7            | Ovarian cancer | In vitro  | Downregulation of PI3K/AKT pathway [382] |
|      |                |                 |                      |                   |                  | Lung cancer    | In vitro  | Enhances apoptosis-inducing factor (AIF) and endonuclease G release [383] |
|      |                |                 |                      |                   |                  | Colon cancer   | In vitro, in vivo | Inhibition of IL-6-mediated STAT3 pathway [384] |
|      |                |                 |                      |                   |                  | Breast cancer  | In vitro  | Downregulation of Nrf2 expression [385] |
|      |                |                 |                      |                   |                  | Pancreatic cancer | In vitro, in vivo | Inhibition of NF-κB and STAT3 pathways [386] |
|      |                |                 |                      |                   |                  | Gallbladder cancer | In vitro  | Activation of caspase-3, -9 and PARP pathway [387] |
| 76   | Withaferin-A   | Steroidal lactone| *Withania somnifera*| C_{28}H_{38}O_{6} | 470.6            | Breast cancer  | In vitro  | Inhibition of TASK-3 expression [388] |
|      |                |                 |                      |                   |                  | Oral cancer    | In vitro  | Upregulation of Bim and Bax expression [389] |
|      |                |                 |                      |                   |                  | Skin cancer    | In vitro  | Activation of TRIM16 [380] |
|      |                |                 |                      |                   |                  | Bone cancer    | In vitro  | Inactivation of Notch-1 signaling [391] |
|      |                |                 |                      |                   |                  | Colon cancer   | In vitro, in vivo | Inhibition of STAT3 Transcriptional activity [392] |
| 77   | Wogonin        | Flavonoid       | *Scutellaria baicalensis*| C_{16}H_{12}O_{5} | 284.26           | Colon cancer  | In vitro  | Increases ER stress, and mediates p53 phosphorylation [393] |
|      |                |                 |                      |                   |                  | Cervical cancer | In vitro  | Inhibition of Cdk4 and cyclin D1 [394] |
|      |                |                 |                      |                   |                  | Lung cancer    | In vitro  | Downregulation of SGK1 protein levels [395] |
|      |                |                 |                      |                   |                  | Bone cancer    | In vitro  | Increases ROS level [396] |
|      |                |                 |                      |                   |                  | Breast cancer  | In vitro  | Activation of ERK and p38 MAPKs pathways [397] |
|      |                |                 |                      |                   |                  | Ovarian cancer | In vitro  | Increase in p53 and decrease in VEGF proteins expression [398] |
| Sr # | Phytochemicals | Chemical Nature | Plant's Source/Origin | Chemical Structure | M: Weight (g/mol) | Cancer Type | Study Type | Targets and Mechanisms |
|------|----------------|-----------------|-----------------------|--------------------|------------------|-------------|------------|------------------------|
| 78   | Xanthatin      | Sesquiterpene lactone | Xanthium strumarium  | C_{15}H_{18}O_{3}  | 246.3           | Skin cancer | In vitro, in vivo | Inhibition of Wnt/β-catenin pathway [399] |
|      |                |                  |                       |                    |                  | Lung cancer | In vitro, in vivo | Inhibition of GSK-3β signaling [400] |
|      |                |                  |                       |                    |                  | Breast cancer | In vitro, in vivo | Inhibition of VEGFR2 signaling [401] |
|      |                |                  |                       |                    |                  | Colon cancer | In vitro     | Inhibition of mTOR pathway [402] |
3. Data Analysis

A total of 78 plant-derived compounds belonging to various families were found to have significant anticancer activity; tested via in vitro and in vivo experiments. Most of these phytochemicals were alkaloids 19 (24%), flavonoids 14 (18%), terpenes 12 (15%), isoflavones 5 (6%), and phenols 5 (6%) (Figure 3).

![Figure 3. Numbers and percentages of anticancer phytochemicals belonging to different phytochemical classes. In this review, most phytochemicals were found to be constituted of alkaloids followed by flavonoids, terpenes, flavones, and phenols. The phytochemical classes that have less than two phytochemicals are included in the miscellaneous class.](image)

Multiple phytochemicals were found to exhibit activity against multiple cancers. Most of the phytochemicals were found to be effective against breast (55), lung and colon (53 each), prostate (45), liver (30), ovarian (27), gastric (24), pancreatic (18), cervical (14), bladder (13), skin (11), oral (9), kidney (7), esophageal and thyroid (6 each), bile duct and brain (5 each), and miscellaneous (10) cancers (Table 3).

| Cancer Type          | Number of Phytochemicals | Cancer Type       | Number of Phytochemicals | Cancer Type          | Number of Phytochemicals |
|----------------------|--------------------------|-------------------|--------------------------|----------------------|--------------------------|
| Breast cancer        | 55                       | Pancreatic cancer | 18                       | Esophageal cancer    | 6                        |
| Colon cancer         | 53                       | Cervical cancer   | 14                       | Thyroid Cancer       | 6                        |
| Lung cancer          | 53                       | Bladder cancer    | 13                       | Bile duct cancer     | 5                        |
| Prostate cancer      | 45                       | Bladder cancer    | 13                       | Brain cancer         | 5                        |
| Liver cancer         | 30                       | Skin cancer       | 11                       | Miscellaneous        | 10                       |
| Ovarian Cancer       | 27                       | Oral cancer       | 9                        | NA                   | NA                       |
| Gastric cancer       | 24                       | Kidney cancer     | 7                        | NA                   | NA                       |

Table 3. Number of effective phytochemicals against different types of cancer.

Of the total phytochemicals, lycopene was found to exhibit activity against 10 different types of cancer; baicalin, corosolic acid, plumbagin, shikonin, and thymoquinone displayed
activity against 9; erianin, evodiamine, gallic acid, and gossypol exerted effects against 8; apigenin, curcumin, luteolin, oridonin, resveratrol, and silibinin had effects against 7; and other phytochemicals showed activity against six or less than six types of cancer (Table 4).

Table 4. Phytochemicals with activity against different number of cancer types.

| Sr # | Phytochemicals                                                                                                                                                                                                 | Effective against Number of Cancer Types |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| 1    | Lycopene                                                                                                                                                                                                     | 10                                     |
| 2    | Baicalin, Corosolic acid, Plumbagin, Shikonin, Thymoquinone                                                                                                                                                  | 9                                      |
| 3    | Erianin, Evodiamine, Gallic acid, Gossypol                                                                                                                                                                   | 8                                      |
| 4    | Apigenin, Curcumin, Luteolin, Oridonin, Resveratrol, Silibinin                                                                                                                                               | 7                                      |
| 5    | Other phytochemicals                                                                                                                                                                                          | ≤6                                     |

Several plant-derived active constituents, such as vincristine, vinblastine, paclitaxel, have been approved by the FDA as therapeutics for different cancers. Several other phytochemicals are currently in clinical trials for the treatment of various cancers (Table 5), and their structures are given (Figure 4).

3.1. Important Anticancer Phytochemicals from the Clinical Trials and Their Structure–Activity Relationship Data

According to a scientific report, phytochemicals may have substantial anticancer properties. Approximately 50% of the drugs approved between 1940 and 2014 were obtained directly or indirectly from natural sources [403]. Some important phytochemicals, currently in clinical trials, that showed good in vitro and in vivo potentials in different types of cancers are described below.

3.2. Curcumin

Curcumin, a lead phytochemical extracted from Curcuma longa, inhibits the growth of human glioma cells by inhibiting numerous cellular and nuclear factors. Curcumin increases the expression of various genes and their products, including p16, p21, and p53, Bax, Elk-1, Erk, c-Jun N-terminal kinase, early growth response protein 1, and caspases-3, -8, and -9, while reducing the expression of Bcl-2, pRB, cyclin D1, mTOR, NF-κB, and p65 [404].

The potent antioxidant property of curcumin is responsible for many of its medicinal actions, including its anticancer activity. The majority of natural antioxidative chemicals are either phenolic or -diketone compounds. But curcumin, is one of the few antioxidative compounds that has both phenolic hydroxy and -diketone groups in a single molecule [405].

In one study, researchers investigated the importance of the phenolic hydroxy groups, and other substituents in the phenyl rings of curcumin and its analogs, to their antioxidant activities by using the three antioxidant bioassays (free radical scavenging activity by the ABTS method, free radical scavenging activity by the DPPH method, and inhibition of lipid peroxidation). In all the three assays, the phenolic curcumin analogs were more potent than the non-phenolic analogs, indicating that the phenolic groups are critical for antioxidant action. Curcumin is thought to be a classic phenolic chain-breaking antioxidant, donating H atoms from phenolic groups [406,407].
| Sr # | Phytochemicals | Source | Cancer Type | Development Stage | Status | Trade Name | NCT Number |
|------|----------------|--------|-------------|-------------------|--------|------------|------------|
| 1    | Vincristine    | Catharanthus roseus | Acute leukemia | FDA approved     | 1963   | Oncovin    | NA         |
| 2    | Paclitaxel     | Taxus braciola      | Late-stage pancreatic cancer | FDA approved     | 2013   | Abraxane® | NA         |
|      |                |         | Advanced non-small cell lung cancer | FDA approved     | 2012   | Abraxane® | NA         |
|      |                |         | Metastatic breast cancer | FDA approved     | 2005   | Abraxane® | NA         |
| 3    | Curcumin       | Curcuma longa     | Prostate cancer | Phase 3 Recruiting, 15 June 2021 | Biocurcumax (BCM-95)® | NCT03769766 |
|      |                |         | Cervical cancer | Phase 2 Not yet recruiting, 25 June 2021 | Curcugreen (BCM-95)® | NCT04294836 |
|      |                |         | Pancreatic cancer | Phase 2 Recruiting, 2020 | NA | NCT00094445 |
|      |                |         | Gastric cancer | Phase 2 Not yet recruiting, 13 January 2022 | Meriva® | NCT02782949 |
|      |                |         | Breast cancer | Phase 1 Recruiting, 23 February 2021 | NA | NCT03980509 |
| 4    | Lycopene       | Solanum lycopersicum | Prostate cancer | Phase 3 Completed, 23 January 2018 | NA | NCT01105338 |
| 5    | Resveratrol    | Polygonum cuspidatum | Multiple myeloma cancer | Phase 2 Terminated (collecting more data) 27 February 2019 | SRT501 | NCT00920556 |
|      |                |         | Colon cancer | Phase 1 Completed, 14 June 2017 | SRT501 | NCT00920803 |
|      |                |         | Neuroendocrine cancer | NA Completed, 18 November 2019 | NA | NCT01476592 |
| 6    | Capsaicin      | Capsicum annuum | Breast cancer | Phase 3 Recruiting, 29 December 2021 | Qutenza® | NCT03794388 |
|      |                |         | Head and neck cancer | Phase 2 Recruiting, 5 August 2021 | Qutenza® | NCT04704453 |
|      |                |         | Prostate cancer | Phase 2 Not yet recruiting, 16 January 2014 | Cayenne | NCT02037464 |
| Sr # | Phytochemicals       | Source                  | Cancer Type                  | Development Stage | Status                                      | Trade Name       | NCT Number       |
|------|----------------------|-------------------------|------------------------------|-------------------|---------------------------------------------|------------------|------------------|
| 7    | Chlorogenic acid     | *Etlingera elatior*     | Lung cancer                  | Phase 2           | Recruiting, 26 November 2018                | NA               | NCT03751592      |
| 8    | Colchicine           | *Colchicum autumnale*   | Liver cancer                 | Phase 2           | Recruiting, 11 February 2020                | Colchicine       | NCT04264260      |
| 9    | Genistein            | *Glycine max*           | Prostate cancer              | Phase 2           | Temporarily suspended, 4 December 2020      | NA               | NCT02766478      |
|      |                      |                         | Colorectal cancer            | Phase 2           | Completed, 10 May 2019                     | Bonistein        | NCT01985763      |
|      |                      |                         | Prostate cancer              | Phase 2           | Completed, 6 August 2019                    | Novasoy 400      | NCT01036321      |
|      |                      |                         | Bladder cancer               | Phase 2           | Completed, 10 June 2021                     | NA               | NCT00118040      |
| 10   | Camptothecin         | *Camptotheca acuminata* | Solid tumor                  | Phase 2           | Completed, 28 May 2020                      | CRLX101          | NCT00333502      |
|      |                      |                         | Stomach and esophageal cancer| Phase 2           | Completed, 1 February 2018                  | CRLX101          | NCT01612546      |
|      |                      |                         | Advanced non-small cell lung cancer| Phase 2 | Completed, 28 May 2020                   | CRLX101          | NCT01380769      |
| 11   | Piperine             | *Piper nigrum*          | Prostate cancer              | Phase 2           | Not yet recruiting, 3 November 2021         | NA               | NCT04731844      |
| 12   | Silibinin            | *Silybum marianum*      | Prostate cancer              | Phase 2           | Completed, 31 March 2014                    | Silibin-Phytosome| NCT00487721      |
| 13   | Quercetin            | *Allium cepa*           | Squamous cell carcinoma      | Phase 2           | Recruiting, 28 October 2021                 | NA               | NCT03476330      |
| 14   | Epigallocatechin gallate | *Camellia sinensis*   | Colon cancer                 | Phase 1           | Recruiting, 15 December 2021               | Teavigo™        | NCT02891538      |
|      |                      |                         | Esophageal cancer            | Phase 1           | Recruiting, 10 September 2021              | NA               | NCT05039983      |
Figure 4. Structures of anticancer phytochemicals approved by FDA or in clinical trials.
In another research study, curcumin analogs were synthesized or isolated from natural sources and evaluated for AR inhibitory activity in prostate cancer cell lines. Among these analogs, few exhibited the greatest inhibitory activity against the transcription of AR, while others showed less or no activity. Based on the bioassay results, researchers showed the SAR of curcumin analogs as anti-AR reagents as follows. (1) The conjugated β-diketone moiety is required for the activity. Saturating or removing the C= C bonds resulted in a decrease or loss of activity, while converting the β-diketone moiety to pyrazole leads to a reduction or loss of activity. (2) When the methylene group in the linker was not substituted, the inhibitory activity was significantly increased by substituting the phenolic hydroxy groups with methoxy or methoxycarbonylmethoxy groups. (3) Adding an ethoxycarbonylethyl group to the central methylene group dramatically improved the anti-AR action of curcumin when the phenyl ring substitution was retained. (4) Anti-AR activity was lost in all electron-withdrawing substitutions in the phenyl rings. The exact mechanism through which curcumin analogs block AR transcription is undisclosed [408–411]. Further initiatives need to be taken to extend the SAR and enhance anti-AR activities of curcumin.

3.3. Epigallocatechin Gallate (EGCG)

EGCG is the chief constituent of green tea that can restore the expression of tumor suppressor genes such as retinoid X receptor-alpha in breast cancer, ultimately preventing breast cancer by binding to other high-affinity proteins such as Zap-70 [412]. EGCG is also found to be effective against lung, colon, and prostate cancers by inducing DNA damage and AMPK signaling and inhibiting Notch1, MMP-2/9, and β-catenin expression [115,117,331].

In EGCG structure, the three aromatic rings are connected by a pyran ring. The structure of EGCG is thought to be responsible for its health-promoting properties. The potent antioxidant effect of catechins is achieved through quinone and semiquinone synthesis, which involves oxidation of phenolic groups with atomic or single electron transfer in the periphery aromatic rings [413,414]. These rings have been linked to a decrease in proteasome activity. Protected analogues are the only ones that suppress proteasome activity. In vitro, dehydroxylation of either one or both periphery aromatic rings, inhibits proteasome inhibitory activity. Furthermore, the apoptotic cell death is induced by these protected analogues in tumor cell-specific manure. These findings showed that the periphery aromatic rings peracetate protected EGCG analogues, have a lot of potential as anti-cancer and cancer-prevention drugs [415]. The first structure–activity correlations between EGCG and heat-shock protein 90 were described and analyzed by Khandelwal et al. His findings suggest that phenolic groups on the aromatic ring, adjacent to pyrin ring, are useful in inhibiting heat-shock protein 90, whereas phenolic substituents on the faraway periphery ring are unfavorable [416]. Finally, when compared to catechins without the 5′-hydroxyl group, the hydroxyl group at the 5′-position in the upper aromatic ring inhibited urease up to 100-fold and also prevented Helicobacter pylori growth in the gut [417].

3.4. Genistein

Genistein, a potent anticancer compound, can be isolated from soybeans, lentils, chickpeas, and beans. It exhibits a pro-apoptotic effect in colon cancer and has a variety of functions: it upregulates Bax and p21, blocks topoisomerase II and NF-κB, and increases the expression of antioxidant enzymes such as glutathione peroxidase [418].

Genistein is a natural flavonoid that has been found to interact with several biological targets. After orally administration, its quick breakdown into inactive metabolites and rapid excretion from the body, are the main disadvantages of using genistein as a chemotherapeutic agent [419]. Therefore, to obtain better bioavailability compounds than genistein, a delayed compound metabolism is required. In one study, it was found that the proportion of metabolites was affected by the nature of the glycosidic bond. The metabolism of genistein derivatives with a more stable C-glycosidic bond was slower than derivatives with an O-glycosidic bond. It was also reported that linking a sugar moiety to the genistein structure increases its metabolism time in the body [420].
In another research work, it has been found that in comparison to the genistein parent molecule, novel genistein glycosyl derivatives with an O-glycosidic or C-glycosidic linkage have better antiproliferative effects. [421,422]. The C-7 or C-4′-hydroxyalkyl ethers of genistein (intermediates in the glycoconjugates synthesis), are found to be more active in preventing tumor cell growth than genistein. Furthermore, biological investigations have also revealed that derivatives with a substituent at the C-7 position inhibit the cell cycle in the G2 phase, whereas derivatives with a substituent at the C-4′ position disrupt the cell cycle in the G1 phase. [421]. It is concluded that the structural modification (hydroxyl group etherification) of genistein, successfully improved its antiproliferative activity.

3.5. Lycopene

Lycopene is a vibrant red pigment found in tomatoes, red carrots, watermelons, and red papaya. It plays a key role in targeting the PI3K/Akt pathway in stomach and pancreatic cancers by suppressing the expression of Bcl-2, an Erk protein. In breast, endometrial, prostate, and colon cancers, lycopene upregulates antioxidant enzymes GSH, GPxn, and GST and eliminates oxidative injury induced by toxins. Lycopene has been demonstrated to affect the growth and progression of HT-29 cells in culture and tumors in animal models by interfering with numerous cellular signal transduction pathways such as those of JNK and NF-κB. Lycopene also prevents infiltration, metastasis, and multiplication of human SW480 colon cancer cells by inhibiting JNK and NF-κB activation, and suppressing the production of COX-2, IL-1, IL-6, IL-10, and iNOS [423,424].

Carotenoids promoted the expression of phase II enzymes by activating the electrophile/antioxidant response element (EpRE/ARE) transcription pathway. Phase II detoxifying enzymes are a key biological method for minimizing cancer risk. By disrupting the inhibitory effect of Keap1 on Nrf2, the key EpRE/ARE activating transcription factor; certain electrophilic phytonutrients have been demonstrated to stimulate the EpRE/ARE system. However, carotenoids like lycopene are hydrophobic, lacking an electrophilic group, which is unlikely to activate Nrf2 and the EpRE/ARE system directly. The active mediators in lycopene’s activation of the EpRE/ARE system are carotenoid oxidation products. Researchers discovered the main structure–activity rules for EpRE/ARE activation using a series of described mono- and di-apocarotenoids that might potentially be produced from in vivo metabolism of carotenoids (lycopene). Such as active molecules are the aldehydes, not acids; the methyl group on the terminal aldehyde, which regulates the reactivity of the conjugated double bond, is responsible for the activity, and the main chain of the molecule is constituted of the dialdehyde’s optimum length (12 carbons). The apocarotenals suppressed breast and prostate cancer cell proliferation with an efficacy comparable to that of EpRE/ARE activation. These findings may provide a molecular explanation for the cancer-preventive properties of carotenoids like lycopene [425,426].

3.6. Resveratrol

Resveratrol, a naturally occurring polyphenol, is found in peanuts, mulberries, grapes, blueberries, and bilberries. It plays a significant role in the treatment of different types of cancers, including colorectal, breast, pancreatic, liver, lung, and prostate cancers, by increasing the expression of Bax and p53 and decreasing the expression of NF-κB, AP-1, Bcl-2, MMPs, cyclins, COX-2, cyclin-dependent kinases, and cytokines. Resveratrol has been recognized to impede angiogenesis and suppress VEGF by decreasing MAP kinase phosphorylation [418].

A research study was carried out to find the structure–activity relationship of resveratrol in cancer. It was observed that the number and position of free phenolic hydroxyl groups have a key role in the anticancer activities of resveratrol. For this purpose, the researchers used different analogs of resveratrol having different phenolic hydroxyl groups for their anticancer activities in T24 cells. They found that the oxyresveratrol (3-OH glycosylated RV, having an extra -OH group than RV) has greater inhibitory effect that RV but polydatin (3-OH glycosylated RV, lack of one -OH group) has a lesser effect than RV.
This showed that the increased number of phenolic hydroxyl groups are responsible for the anticancer activity of RV [427]. Herath et al. proved the theory by discovering that when the hydroxyl groups in RV were replaced, the drug’s pharmacological activity decreased [428]. Furthermore, Miksits et al. found that all of RV’s sulfated metabolites were less effective against various cancer cell lines [309]. This suggests that the anti-tumor efficacy of RV can be affected by the conjugation of phenolic hydroxyl groups with sulfuric acid. Hence, again it is proved that the free phenolic hydroxyl groups are important for antitumor effect of RV.

Currently, several investigations on plant-based drugs to treat cancer are ongoing. Some well-known and effective phytochemicals, such as vincristine, were approved by the FDA in 1963 to treat acute leukemia (brand name, Oncovin). Furthermore, paclitaxel was approved for the treatment of metastatic breast cancer, advanced lung cancer, and pancreatic cancer in 2005, 2012, and 2013, respectively, under the brand name, Abraxane. Curcumin, lycopene, and capsaicin, which are under phase-III trials for prostate and breast cancers, are promising candidates for cancer therapy. Quercetin, genistein, silybinin, and EGCG are undergoing clinical trials or treatment for various types of cancers.

This study of anticancer plant-derived phytochemicals will help ethnomedicine and ethnopharmacology investigations, resulting in better outcomes for the medical potential of natural resources. Various phytochemicals highlighted in this review could be further investigated in clinical trials, enabling the availability of more effective anticancer medicines with fewer adverse effects. This study will be beneficial to researchers working on or interested in the discovery of plant-based medicines for treatment of various cancers.

4. Conclusions

Researchers have found multiple synthetic drugs for the treatment of cancer, but anticancer drugs are costly and have some major adverse effects like anemia, vital organs damage, and hair and nail loss. Keeping in mind these drawbacks, we searched multiple papers on natural anticancer compounds, their mechanisms, clinicals trials and SAR data of important phytochemicals. The epidemiology data showed that the breast and lung cancers have the highest mortality and prevalence rates. In this study, we found that majority of anticancer compounds belong to alkaloids and flavonoids classes, and the highest number of phytochemicals were found to be effective against breast and lung cancers, which give us a chance to try these phytochemicals in clinical trials and discover some plant-based drugs that control these high spreading cancers. To discover effective anticancer treatments with less side effects and less cost, the world must rely upon, and conduct more research on natural resources, especially plants and their active constituents.

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Abbreviations

AIF Apoptosis-inducing factor  
Apa-f-1 Apoptotic protease activating factor 1  
ATF4 Activating transcription factor 4  
Bcl-Xl B-cell lymphoma-extra-large  
CCL2 Chemokine (C-C motif) ligand 2  
CDK Cyclin-dependent kinases  
CHOP C/EBP homologous protein  
CREB cAMP-response element binding protein  
CXCR4 C-X-C chemokine receptor type 4  
DR5 Death receptor 5  
ER Endoplasmic reticulum  
FAK Focal adhesion kinase  
FOXA2 Forkhead box protein A2  
GADD45B Growth arrest and DNA-damage-inducible, beta protein  
GLUT1 Glucose transporter 1  
H2AX H2A histone family member X  
HIF-2α Hypoxia inducible factor 2 alpha  
HMGB1 High mobility group box 1 protein  
HOXD3 Homeobox D3  
iNOS Inducible nitric oxide synthase  
IκBα IkappaB alpha  
IκK-α Inhibitory-κB kinase alpha  
JNK Jun N-terminal kinase  
Keap1 Kelch-like ECH-associated protein 1  
LOX Lysyl oxidase  
MEK MAPK/ERK kinase  
mTOR Mammalian target of rapamycin  
NBR1 Neighbor of BRCA1 gene 1  
NF-κB Nuclear factor kappa light-chain enhancer of activated B cells  
Nrf2 Nuclear factor erythroid 2-related factor 2  
PTEN Phosphatase and tensin homolog deleted in chromosome 10  
PTEN Phosphatase and tensin homolog deleted in chromosome 10  
Raf Rapidly accelerated aibrosarcoma  
RASSF6 Ras-association domain family  
RASSF6 Ras-association domain family  
RhoA Ras-homolog family member A  
ROS Reactive oxygen species  
RIP1 Receptor interacting protein 1  
ROCK1 Rho-associated protein kinase 1  
SGK1 Serum/glucocorticoid regulated kinase 1  
Skp2 S-phase kinase associated protein 2  
Skp2 S-phase kinase associated protein 2  
SGK1 Serum/glucocorticoid regulated kinase 1  
Top1 Topoisomerase 1  
Topoisomerase 1  
TRA1 Tumor necrosis factor-α  
TNF-α Tumor necrosis factor-beta1  
TOP2A Topoisomerase 2  
TOP2A Topoisomerase 2  
TNF-α Tumor necrosis factor-alpha  
TRAIL TNF-related apoptosis-inducing ligand  
TRIM16 Tripartite motif-containing protein 16  
Wnt Wingless-related integration site  
XIAP X-linked inhibitor of apoptosis protein  
X-linked inhibitor of apoptosis protein  

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