Mode of action of some bioactive compounds with anticancer activity

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ABSTRACT

Cancer is characterized by the development of cells that are unlike normal cells and they divide rapidly and also corrupt and destroy normal tissues in the body. Cancer cells possess the ability to spread through the body and cause damage. Cancer is caused by the mutation of DNA. The estimate of cancer cases worldwide as of 202 has risen to 19.3 million and almost 10.0 million cancer deaths. Cancer has several means with which it sustains its growth. Cancerous action in the body involves unchecked, uncontrolled cell division and metastasis which is characterized by incading of other cells and tissues in the body. This is caused by a series of mutation in the genes of proteins that regulate the cell cycle and some other processes in the cell. These mutations suppress the ability of the cell to stop the cell cycle and promote cell division which causes continuous and uncontrolled division of cells. Bioactive compounds can be derived from plants, animals, or other sources and they have a wide range of biological and functional activities like anti-inflammatory, antiviral, anticancer, and antidiabetic activities; with the plant sources widely researched into for anticancer activities. Bioactive compounds have in recent years gained popularity in their role against cancer. This current study aims to review the mechanisms of action of anticancer activity of some of these bioactive compounds.

Keywords: anticancer, bioactive compounds, cancer, genistein, mechanism
INTRODUCTION

Cancer: Cancer is characterized by the development of cells that are unlike normal cells and they divide rapidly and also corrupt and destroy normal tissues in the body. Cancer cells possess the ability to spread through the body and cause damage [1]. Cancer is caused by the mutation of DNA. The estimate of cancer cases worldwide as of 2020 has risen to 19.3 million and almost 10.0 million cancer deaths [2]. Cancer has several means with which it sustains its growth.

Cancerous action in the body involves unchecked and uncontrolled cell division and metastasis which is characterized by invading of other cells and tissues in the body. This is caused by a series of mutations in the genes of proteins that regulate the cell cycle and some other processes in the cell. These mutations suppress the ability of the cell to stop the cell cycle and promote cell division which causes continuous and uncontrolled division of cells [3].

There are normal genes that promote cell growth and cell division, these are the proto-oncogenes which are normal genes that promote cell growth and mitosis, whereas tumor suppressor genes repress cell growth. These proto-oncogenes are usually mutated by carcinogens to become oncogenes that produce excessive levels of growth-promoting proteins [4].

On the other hand, natural tumor suppressor genes which are transcription factors that suppress mitosis and cell growth to allow DNA repair, are mutated in cancer making them unable to checkmate cancer. For example,
p53, which is a tumor protein gene that codes for a protein that regulates the cell cycle and plays a role in cell division and cell death is mutated in cancer [5].

Following continuous mutations of proto-oncogenes and suppressor genes that permit unregulated cell growth, cancer begins to manifest [6]. Therefore cancer cells promote characteristics or activities that favour their growth but hinder the activities that oppose their growth. These characteristics include the ability to avoid apoptosis, increase cell division, alter cell differentiation, growth-factor self-sufficient, resistance to anti-growth factors, increase cell proliferation and metastasis, lose contact inhibition and promote angiogenesis (Fig 1) [7].

![Fig 1. Mechanisms of Cancer Development](image)

**Bioactive Compounds**: Bioactive compounds have in recent years gained popularity in their role against cancer [8]. These bioactive agents can be grouped into different classes. Some of these bioactive compounds and their mode of action against cancer are illustrated below:

**Flavonoid**: Flavonoids are polyphenolic compounds that can be found in fruits, vegetables, green tea, wine, and cocoa. Some flavonoids have been shown to possess a wide variety of anti-cancer effects [9]. An example of a flavonoid with anti-cancer effect is genistein.

![Fig 2. Chemical structure of Genistein](image)
Genistein: Genistein (4,5,7-trihydroxyisoflavone) is an isoflavone under the flavonoid family (Fig 2). It is obtained from soy products like soybeans. Other sources of genistein are dates and raisins [11]. It has been observed that in Asian countries, especially Japan and China the occurrence of breast cancer in women and prostate cancer in men was less compared to western countries like the United States. This was because these Asian countries have a higher consumption of soy products which is the richest source of genistein. It also has anti-cancer effect on other types of cancer [12].

Genistein has various mechanisms to hinder the progression of cancer. Genistein induces apoptosis of the cells by blebbing of the cell membrane, fragmentation of the cell’s DNA, mitigation of attachment of cells, change of cell shape and structure, contraction of the cytoplasm, and other biological changes detrimental to the cell (Fig 3) [13].

Genistein modulates several steps critical in processes occurring in the cell. There are various means by which genistein enhances apoptosis in cancer cells. Genistein induces caspases such as caspase-3 and caspase-9 which play significant roles in the apoptosis of a cell [14].

In an in vitro study involving colon cancer cell, genistein triggered apoptotic cell death by inhibiting the NF-κB pathway which mediates the induction of pro-inflammatory gene [15]. In breast cancer cell lines, genistein combined with equol, a bioactive metabolite of daidzein influenced the levels of Bax, a pro-apoptotic protein that promotes apoptosis by increasing Bax and reduced the levels of Bcl-2, an anti-apoptotic protein whose main function is to work against Bax and hinder apoptosis [16]. In a melanoma cell line, p38 MAPK signaling pathway which responds to stress stimuli was also modulated by genistein leading to the endoplasmic reticulum of cancer cells been affected by genistein. Upregulation of GRP78, a molecular chaperon involved in protein folding and C/EBP homologous by genistein, increased endoplasmic reticulum stress resulting in apoptosis [17].

In hepatocellular carcinoma, genistein discontinued the supply of oxygen to cancer cells by inactivating a glucose transporter in the cell called GLUT 1 by down-regulating hypoxia-inducible factor-1α thereby mitigating aerobic glycolysis in the cells which in turn suffocated the cancer cell eventually leading to apoptosis [18]. Genistein caused the overactivity of Calpain 1 which led to the lysosomal membrane being very permeable thereby triggering the release of cathepsin B and DNase II resulting in damaged DNA of the cancer cells and therefore apoptosis in human breast cancer MCF-7 cell lines [19].

The proliferation of cancer cells usually depends on some inflammatory markers. Therefore, in an in vitro study on human keratinocytes (HaCaT cell line), genistein suppressed tumor necrosis factor-α (TNF-α)-induced nuclear factor-κB (NF-κB) translocation [20]. It also mitigated the phosphorylation of IκB kinase-α/β and induced the activation of caspase 8 by promoting the attachment of Fas/TNF, a death receptor to FasL/TNFR1, the combination of this ligand to the receptor will trigger apoptotic reactions [21].
Fig 3. Genistein mechanism of inducing apoptosis in cancer cells [21]

Asides from inducing cell death in cancer cells, genistein utilizes other mechanisms like halting or reducing vascularization of the cancer-ridden area thereby starving cancer cells. Cancer cells also need supply of blood and nutrients, therefore anything that hinders them from receiving the required nutrients can be a promising method to alleviate the rampage of cancer. The development of new blood vessels is known as angiogenesis. Genistein has been shown in a colon cancer studies to possess antiangiogenic properties where it was implicated in the hindrance of vascular endothelial growth factor (VEGF) [22]. Vascular endothelial growth factor is a signalling protein that promotes the growth of new blood vessels, therefore by inhibiting the activities of VEGF, genistein hinders angiogenesis. Genistein also hindered angiogenesis by down-regulating matrix metalloprotease-2 (MMP-2), matrix metalloprotease-9 (MMP-9) expression, and urokinase plasminogen activator. It enhanced components that inhibit angiogenesis such as angiotatin, plasminogen activator inhibitor-1, thrombospondin-1, and endostatin. Activation of these inhibitors of vascularization hindered the formation of new blood vessels. This shows that genistein by hindering the growth of blood vessels can stop the growth of cancer cells [23].

Halting of the cell cycle is another mechanism by which genistein mitigates cancer. Cancer cells undergo proliferation because they need to grow and divide. Genistein prevented the multiplication of the cells by halting the cell cycle. In human gastric carcinoma, genistein inhibited the growth of cancer cells by halting the cell cycle succession at G2-M thereby stopping the division of the cells [22].

Genistein also initiated the activation of the ATM/ATR-p53-p21 signaling pathway via the phosphorylation of this pathway leading to a halt in the cell cycle (Fig 4). Platelet-derived growth factor that
stimulates cells to begin the cell cycle was inhibited by genistein. Genistein also regulated several regulatory proteins in the cell cycle by modulating their expression in the cell [21]. For instance, in esophageal carcinoma cells, genistein down-regulated the expression of Cdc25C which is a drive for cell cycle. Genistein downregulated cyclin which activates cyclin-dependent kinase by inhibiting the binding of cyclin to cyclin-dependent kinase which in turn inhibited the expression cyclin-dependent kinase. Another way genistein hindered cyclin-dependent kinase was by upregulating the expression of its inhibitor p21WAF/CIP1 which hinders cyclin-dependent kinase from binding to cyclin-cyclin-dependent kinase complexes before inhibiting their activity [24]. Aside from these, genistein triggered cell arrest by modulating mitogen-activated protein kinase (MAPK) thereby down-regulating cyclin, Cdc25C, and cyclin-dependent kinase. Genistein also inactivated cyclin-dependent kinase by activating Chk1 and Chk2 which are checkpoint kinases that can cause cell cycle arrest [25].

**Fig 4.** Mechanism by which Genistein halts cell cycle of cancer cells [21]

Furthermore, cancer cells depend on their ability to spread to other regions. Studies have shown that genistein has the potential to stop metastasis which is the spread of cancer cells. Genistein inhibited several factors implicated in cancer cells metastasis such as COX-2, matrix metalloproteinase-9, Ang-1, vasodilator-stimulated phosphoprotein, and vascular endothelial growth factor. Genistein reduced the ability of the cells to adhere together by reducing the expression of focal adhesion kinase (FAK) [21]. Genistein also reduced the expression of an epithelial-to-mesenchymal transition transcription factor. In an in vitro study involving melanoma cells, genistein down-regulated some other factors like α-actinin, vinculin, p-paxillin, α-actinin and tensin-2 [26].

This shows that the mechanisms by which genistein acts in its anticancer effect are quite vast and unlike most anticancer drugs or treatment that are more specific. Therefore genistein treatment is a promising path in fighting against cancer.

Other flavonoids that have shown considerable anticancer properties are cyanidin, luteolin, peonidin, malvidin, daidzein, pelargonidin, delphinidin, taxol, and vinblastine [9].
**Alkaloid:** Alkaloids are organic nitrogen derivatives. They can be found in coffee, cacao, and teas like green tea. These alkaloids possess anticancer effects. An example of an alkaloid exhibiting anticancer effect is berberine.

**Berberine:** Berberine is an isoquinoline protoalkaloid (Fig 5). Other isoquinoline alkaloids are columbamine, dehydrocorydaline, palmatine, jatrorrhizine and epiberberine, and coptisine [27]. Berberine can be found in plants and herbs like tree turmeric (berberis aristata), goldenseal (hydrastis cacadenis), oregon grape (berberis aquifolium), barberry (berberis vulgaris), huanglian (coptidis rhizome), European berberry, greater celandine, and phellodendron [28].

![Chemical structure of Berberine](image)

**Fig 5.** Chemical structure of Berberine [29]

Berberine has various mechanisms of exhibiting its anti-cancer properties such as halting metastasis and cell cycle of cancer cells, anti-inflammatory and anti-oxidant activities, inhibiting angiogenesis and reduction of transcription factors (Fig 6). Cancer cells utilize cytokines as a means of contaminating surrounding cells. Berberine however stomps on the inflammatory path of cancer cells by downregulating pathways that can further fuel inflammation like the caspase-1/IL-1β signaling pathway [32]. Berberine also stopped cancer cells metastasis in uterine cancer cell lines by reducing the expression of transcription factor snail-1 [33] and directly affecting microRNAs. MicroRNAs have been implicated at the early and developmental stages of cancer cells. In some cancer cells such as hepatoma cells of the liver, berberine modulated the transcriptional activation of p21 and GADD45α by up-regulating the expression of miR-23a [34]. The multiplication and migration of cancer cells were inhibited by berberine through the down-regulation of GRP78 expression [35].

Berberine induced Nrf2 activation, decreased oxidized LDL-induced inflammation by regulating the AMPK/mTOR signaling pathway thereby reducing inflammation [36]. Anti-inflammatory activities of berberine were also exerted by stimulating the AMPKα-SIRT-1-PGC-1α signaling pathway and inhibiting the mitogen-activated protein kinase 4 -SAPK/JNK-C-JUN. Down-regulation of TNFα and IL-6 was also observed in the treatment with berberine [37].

Berberine may also serve as an anti-oxidant because it increased the activities of catalase and glutathione peroxidase enzymes in melanoma cells [38]. Some studies also show that berberine reduced oxidative injury by suppressing reactive oxygen species through the inhibition of mTOR, P13K, and AKT pathways which could increase the risk of cancer [39].

Angiogenesis was hindered by berberine in cancer by downregulating the expression of vascular endothelial growth factor (VEGF), IL-2, IL-6, and TIMP which play key roles in the formation of new blood vessels [40]. Cancer utilizes these blood vessels to get nutrients that support the growth of cancer cells if not mitigated. In an in vitro study on 22RV1 human prostate cancer cell, berberine reduced the expression of matrix metalloproteinase-2 (MM2) and matrix metalloproteinase-9 (MM9) by inhibiting the COX-2, PGE2-JAK2, and STAT3 signaling pathways. Inhibition of the expression of MMP-2 and MMP-9 was also done by downregulation of TGF-β1.
These along with the targeting of ephrin-B2 hindered cell spreading and proliferation [41].

In human gastric, colon, liver and lung cancer cells, berberine enhanced apoptosis in cancer cells preventing the progression of the cancer cells. It stimulated cell death by increasing the activity of various factors in the cell leading to a series of reactions eventually causing the death of the cells. Berberine activated caspase-3 thereby inhibiting the expression of Bcl-2 and enhancing the expression of caspase-8 and caspase-9 [42]. The caspases were activated by berberine through an elevated cytochrome C level, AMPK activation, and elevated production of ROS. The activation of JNK and p38 also increased p53 phosphorylation promoting the entry of Bax and Bim into mitochondria, resulting in the heightened permeability of the mitochondrial membrane. All these eventually leading to apoptosis. Berberine also induced the expression of ATF3 protein by increasing the transcription of p53 transcription thereby promoting cell apoptosis [43].

The cell cycle in cancer cells was also halted by berberine, this hindered the growth and multiplication of the cell thereby slowing down or stopping their proliferation. Berberine achieved the inhibition of the cell cycle by modulating cyclin, therefore, inhibiting cyclin-dependent kinase (CDK4) expression. Berberine utilized this mechanism in melanoma cells to stop cell growth by modulating PI3K, Akt and p38 activation thereby up-regulating p21 and p53 expression resulting in the arrest of the G2/M phase in the cell cycle. Berberine prevented the transition from G1 phase to S phase by inhibiting the phosphorylation of Rb protein, which stopped the detachment of E2F, a transcriptional activator from Rb [38]. These mechanisms are represented in Fig 7 and through all these mechanisms berberine can be used as an anticancer agent although more research needs to be carried out.

Other alkaloids that possess anticancer properties include evodiamine, piperine, sanguinarine, tetrandrine, noscapine, and mutrine.
Fig 7. Mechanism of anti-cancer activity of Berberine [31]

**Terpene:** Terpenes are natural isoprenoid derivatives. Terpenes can be found in plants like thyme, Cannabis, tea (Melaleuca alternifolia), Spanish sage (Salvia lavandulifolia), citrus fruits like lemon, orange, mandarin [44].

**Cannabis (Myrcene):** Cannabis is from Cannabis sativa plant (Fig 8). Cannabis is most abundant in myrcene. Myrcene can also be found in parsley, hops, thyme, and lemongrass [45].

Cannabis has the potential to mitigate cancer however because of its components which cause undesirable effects, the use of it has been skeptical. The two main cannabinoids in cannabis are Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) with both of them portraying different pharmacological activities (Fig 9). Utilizing Δ9-THC has been associated with some unfavourable effects like tachycardia, anxiety, altered cognitive perception, and psychoactivity that can lead to addiction. Such undesirable effects however are not seen with CBD [46]. CBD has shown potential anticancer properties.

Fig 8. Cannabis plant [45]
CBD has been shown to have anticancer effects on several types of cancer such as lung cancer, glioma, thyroid, lymphoma, skin, pancreas, uterus, breast, prostate, and colorectal carcinoma [48]. Over the years more anticancer mechanisms of cannabinoids are emerging, showing their ability to interfere with cancer neovascularization, cancer cell migration, adhesion, invasion, and metastasis [49].

Although CBD has been effective against several types of cancer, most research has been centered on the effect of CBD in glioma cells. Cannabinoids have been shown to influence the death of glioma cells by apoptosis via CB1- and CB2- and TRPV1-independent stimulation, upregulating cytochrome c, caspase 3, and reducing glutathione. Stimulation of CB1- and CB2- and TRPV1 receptors upregulated COX-2 in lung and cervical cancers, this is also related to its pro-apoptotic activity. Cancer invasiveness is inhibited by the formation of inhibitory complexes of TIMP-1 with MMP-2 and MMP-9. Cannabinoids drive the intracellular accumulation of ceramide to activate Raf1/ERK signaling leading to the production of damaging cellular reactive oxygen species (ROS). This drives genotoxic stress and apoptosis in glioma cells. Treatment with cannabinoids increased p8, a stress-regulated protein thereby leading to the inhibition of the Akt/mammalian target of rapamycin (mTOR) cell signalling axis and the activation of caspase cascades. Activation of caspase cascades induced apoptosis in cancer cells. Cannabinoid downregulated the expression of anti-apoptotic protein Bcl-2 which hindered apoptosis while upregulating the expression of apoptosis regulator BAX and cellular tumour antigen p53 (TP53). It can also promote apoptosis through tumour necrosis factor-α (TNF-α) mediated de novo synthesis of ceramide [50].

Endoplasmic reticulum stress-related transcription factors ATF4 and CHOP, and the pseudokinase tribbles homologue 3 (TRIB3) are also targeted by cannabinoids which leads to inhibition of the mammalian target of rapamycin complex 1 (mTORC1) leading to apoptosis via autophagy-mediated cell death. Cannabinoid promoted inhibition of the interaction of TRIB3 with a pro-survival kinase, AKT37, and AKT38. This eventually leads to the death of cancer cells [51].

Asides from glioma cells, in hepatocellular carcinoma cells, cannabinoid also induced endoplasmic reticulum stress-dependent activation of calcium/calcmodulin-dependent protein kinase 2β and AMP-activated protein kinase also leading to cell death. The cannabinoid-
mediated inhibition of AKT promoted the arrest of the cell cycle in cancer cells of breast cancer and melanoma cancer. It also induced apoptosis by decreasing phosphorylation of the pro-apoptotic protein Bcl2-associated agonist of cell death and activation of the cyclin-dependent kinase inhibitory proteins p21 and p27. This resulted in subsequently decreased phosphorylation of the retinoblastoma protein causing the arrest of the cell cycle, then cell death [52].

Cannabinoid achieved its antiangiogenic properties by blocking the activation of the vascular endothelial growth factor pathway which induces angiogenesis. Vascular endothelial growth factor receptors 1 & 2 are also downregulated by cannabinoids [53]. In human prostate cancer cell lines, CBD downregulated CB1, CB2, PSA, VEGF, IL-6, and IL-8 demonstrating its anti-inflammatory activities [54]. These mechanisms of action of CBD are highlighted in Fig 10.

Aside from myrcene, there are other terpenes present in cannabis which include α-pinene, and β-caryophyllene [55].

Another terpene that has gained attention for its potential in cancer mitigation is lycopene. Lycopene is a tetraterpene. It is part of the carotenoid family of compounds [57]. Lycopene is found mostly in tomatoes [58]. Lycopene’s mechanism in combating cancer includes most noticeably antioxidant properties, obstruction of insulin-like growth factor 1 receptor signaling pathways, decreased lipid oxidation, inhibition of cancer cell proliferation, apoptosis, increased gap-junctional communication and hindering cell cycle progression. It also inhibits cell invasion, angiogenesis, and metastasis [59].

Other terpenes with anti-cancer prospects are Limonene and Canthardin which are monoterpenes,
Artemisin which is a sesquiterpene, Tanshiron 11A, Triptolide, Pseudolanic acid B, Oridorin and Adrographolide which are diterpenes, Celestrol, cucurbitacin, Alisol B, and Pachymic acid which are triterpenes.

**Tannin:** Tannins are polyphenols with higher molecular weight [60]. Plants in which tannin can be found include barks of Red Angico (Anadenanthera macrocarpa), Jabuticaba (Myrciaria jabuticaba) and Umbu (Spondias tuberosa) [61]. It can also be found in wattle (Acacia mearnsii) [62].

**Gallic Acid:** Gallic acid is a trihydroxybenzoic acid, also known as 3, 4, 5-trihydroxybenzoic acid. It belongs to the group of hydrolyzable tannins (Fig 11). Gallic acid is present in food such as plums, grapes, mango, gallnuts, cashew nut, hazelnut, berries, walnut, tea, and wine [63].

Gallic acid and its derivatives are effective against cancer. It has been shown to have the ability to combat various kinds of cancer like colon cancer, breast cancer, liver cancer, esophageal cancer, leukemia e.t.c.
Studies on the anti-cancer mechanism of gallic acid on human colon adenocarcinoma COLO 205 cells showed fragmentation of DNA to oligonucleosomal fragments after gallic acid treatment [66]. Gallic acid also induced apoptosis of cancer cells. In a study on HCT-15 human colon cancer cells, gallic acid caused the rounding and shrinking of the cell and also detachment from the substratum. These reduced the viability of the cancer cells leading to the death of the cells. The study also showed antiproliferative effect of gallic acid against U-2OS osteosarcoma cells. The levels of p-JNK and p-ERK1/2 kinase decreased while the level of p38 kinase increased after the treatment with gallic acid. This indicated that gallic acid induced apoptosis of osteosarcoma cells through the inactivation of JNK and ERK1/2 kinase pathways and the activation of p38 kinase pathway. CD31 which promotes angiogenesis was significantly less, illustrating the anti-angiogenetic effect of gallic acid in U-2OS cells. GRB2, PI3K, AKT/PKB, PKC, p38, ERK1/2, JNK, NF-κB p65 were also down-regulated by gallic acid and it inhibited the activities of AKT, IKK, PKC, MMP-2, and MMP-9 proteins [67].

Gallic acid diminished the growth of breast cancer cells by increasing p27 and p21 while decreasing the activity of cyclin A, CDK2, cyclin B1, and cdc2/CDK1. This caused consistent halting of cells at the G2/M phase, therefore, obstructing proliferation [65]. Gallic acid also induced apoptosis by enhancing the cleavage of Poly-ADP-ribose polymerase 1 and promoting mitochondrial membrane depolarization and causing morphological alteration. Gallic acid treatment in studies showed that activated caspase-3, caspase-9, and ROS, elevated Bax expression, and reduced mitochondrial membrane integrity. Overexpression of Bcl-2 in cancer cells and phosphorylation of c-Jun N-terminal protein kinase also occurred [68].

Another study showed cytotoxic effect of gallic acids in leukemia. The study portrayed apoptosis of leukemia cells after treatment with gallic acid. Apoptosis of cells was coupled with cell cycle arrest at the G0/G1 phase [69]. Gallic acid also caused the inhibition of ribonucleotide reductase [70].

Other tannins that showed anticancer properties are proanthocyanidin, tarragallotannin, and caffetannin [71].

**CONCLUSION**

Cancer can affect any part of the body and is one of the primary causes of death globally. Radiotherapy, surgery and chemotherapy are currently being utilized in the management of cancer but they have been discovered to have side effects and cannot effectively cure this disease. Bioactive compounds are a very promising focus in the prevention and treatment of cancer. Some of these compounds have been discovered to have positive effects in the treatment of breast cancer, prostate cancer, colon cancer, lung cancer, esophageal cancer, cervical cancer, leukemia, melanoma and glioma cells. These phytochemicals possess diverse mechanisms with which they can be effective against cancer. In this review, the mechanisms of action of some bioactive compounds; genistein, berberine, gallic acid and CBD were outlined which include: induction of apoptosis in the cancer cells by fragmentation of the DNA, preventing angiogenesis, halting the cell cycle and stopping metastasis of the cancer cells, inhibiting cell proliferation. As a result of these mechanisms of action, these bioactive compounds could be great prospects in the development of therapeutic drugs effective in the treatment of different types of cancer. Most of these studies are however *in vitro* studies involving cancer cell cultures therefore, more clinical studies are needed to validate the usefulness of these bioactive compounds in cancer management.

**List of Abbreviations:** DNA: Deoxyribonucleic acid; NF-κB: Nuclear factor kappa B; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma-2; MAPK: Mitogen-activated protein kinase
kinase; C/EBP: CCAAT-enhancer-binding proteins; GRP78: Glucose Regulated Protein-78; ATM/ATR: Ataxia telangiectasia mutated (ATM) rad3-related (ATR); Chk: Checkpoint kinase, COX: Cyclooxygenase; Ang-1: Angiopoietin-1; FAK: Focal adhesion kinase; IL: Interleukin; miR: MicroRNAs; Nrf2: Nuclear factor erythroid2-related factor 2; AMPK/mTOR: /mammalian target of rapamycin; TNFα: Tumour necrosis factor-α; MMP: Metalloproteinase, TGF:Transforming growth factor; MMP: Matrix metalloproteinases; TIMP: Tissue inhibitors of matrix metalloproteinases; CHOP: C/EBP Homologous Protein; ERK: extracellular signal-regulated kinases; JNK-c:Jun N-terminal kinases; MAPK: mitogen-activated protein kinase; MAPKAPK2: MAP kinase activated protein kinase 2

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