Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3485-3505 | ISSN:2251-6727

A Review on Plant Based Phytoconstituents for the Management of Breast Cancer

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(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS
Breast cancer, plant phytoconstituents, challenges and future aspects

ABSTRACT:
One of the main causes of cancer-related fatalities worldwide is breast cancer, poses challenges in treatment due to resistance and side effects of hormone therapy, surgery, chemotherapy, and radiation. Despite their efficacy, these modalities become less effective over time, highlighting the need for alternative approaches to improve outcomes in breast cancer management. Adopting a supplementary treatment strategy, however, can be a significant solution in this case because it is well known that substances obtained from natural sources have strong anticancer properties. Plant-based products have been demonstrated to be excellent sources of cutting- edge anti-cancer medications throughout medical history. Ongoing research focuses on identifying medicinal plants and natural products for novel breast cancer therapies. Numerous plant-derived compounds have been evaluated, showing promise in breast cancer treatment. This exploration underscores the potential of natural sources in developing effective therapeutic strategies against breast cancer. Therefore, it is expected that plants may offer prospective bioactive substances for the creation of novel "leads" in the fight against breast cancer. Phytoconstituents derived from plants are useful for alternative breast cancer therapy due to their activities and their synergistic activity with other medications.

1. Introduction:

Cancer poses a significant health risk in contemporary society, impacting individuals worldwide with its complex and multifaceted challenges. The increasing levels of pollution and exposure to carcinogens in many facets of our lives have made cancer a major worry.[1] Surgical procedures, chemotherapy, anti-cancer medications, hormone therapy, and radiation therapy are all part of conventional treatment; however, side effects, drug resistance, and relapse make it very difficult to select an appropriate therapeutic approach.
Scientists are currently investigating many alternative drugs and therapy techniques to addressthese issues.

Up to now, natural chemicals have been used in the development of more than 50% of pharmaceuticals; of these, 75% of anticancer medications have been created using natural components originating from plants.[2]
Numerous physiological pathways may be stimulated by natural products derived from varioussources, which may prove advantageous in the treatment of challenging diseases like cancer. According to recent research, natural products can successfully target certain breast cancer-related pathways, which may be helpful for managing or treating the condition.[3,4] Phytochemicals, bioactive agents, active secondary metabolites, etc. are examples of natural products.
Breast cancer is classified as either ER-positive or ER-negative based on the presence of the oestrogen receptor. Breast cancer is stratified into various molecular subtypes based on markers like human epidermal growth factor receptor 2 (HER2) and progesterone receptor. Subtypes include HER2-positive, luminal A, luminal B, and basal-like (triple-negative) breast cancer, aiding in personalized

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 3485-3505 | ISSN:2251-6727

treatment approaches.[5,6]

Numerous research have also been conducted on natural chemical-based therapy for subtypesof breast cancer. When utilised in BrCa therapy, organic medications are frequently quicker, less expensive, safer, and less harmful. Apoptosis and chemo-sensitization can be induced by certain natural combinations.

The present study focuses on the ongoing discourse surrounding the utilization of different natural products for breast cancer treatment, drawing insights from published research data.[7,8]

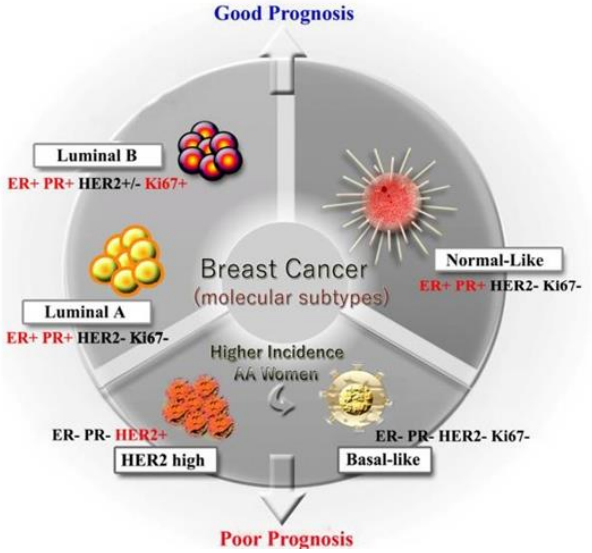

Figure 1. Subtypes of Breast Cancer

2. Natural Compounds as Therapeutics

1. ***3,3-Diindolylmethane***: Broccoli, cabbage, and cauliflower are examples of cruciferous vegetables that are rich in the natural chemical DIM. It is the main byproduct of indole-3- carbinol's acid condensation.

When the atmosphere is acidic, the stomach converts I3C to DIM. Based on experimental evidence, DIM was shown to suppress COX-2 production in human breast cancer cells that was triggered by the aryl hydrocarbon receptor. According to Fan et al., DIM activated Brca1's phosphorylation during oxidative stress and carried out shielding functions. Subsequent research revealed DIM suppresses the expression of genes that express angiogenesis, such as hypoxia-inducible factor-1 and remaining. The Ahmad group also noticed a similar outcome with Taxotere, where DIM also targeted FoxM1.[9,10] As a result, DIM showed favourable effects on oestrogen metabolism and specifically increased the chemosensitivity of tamoxifen in randomised, placebo-controlled trial tests. Wang and colleagues demonstrated that DIM enhanced the formation of ROS within cells, exposed cells to UV light, and caused apoptosis by stopping the growth of cells at the G2/M stage. In the mouse model, significant tumour suppression by DIM was also reported.[11,12]

Although DIM has demonstrated a great deal of effectiveness in treating breast cancer, Marques et al. have demonstrated that, when DIM is taken as a dietary supplement, it can cause cellular proliferation at concentrations of up to 10 μM through turning on the oestrogen receptor

α signalling mechanisms where estradiol is absent. To understand the unanticipated negative consequences of DIM supplementation for the prevention, treatment, or diagnosis of human breast cancer, more research should be necessary. The chemokine CXCR4, which is responsible for the spread of breast cancer through an ER-dependent pathway, is suppressed by 3,30-Diindolylmethane (DIM).[13,14]

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JCHR (2024) 14(2), 3485-3505 | ISSN:2251-6727

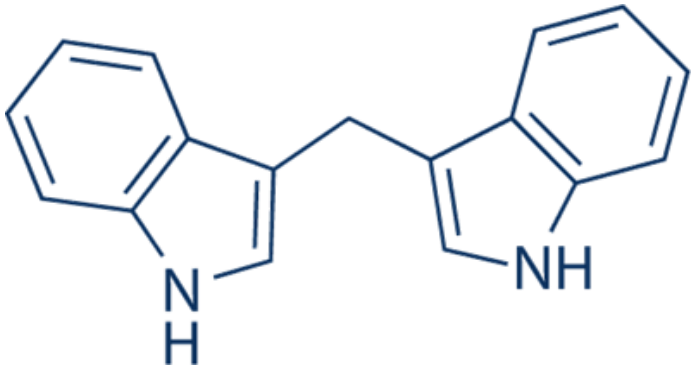

Figure 2. 3,3-Diindolylmethane

2. *Biochanin A.* Red clover is the source of the isoflavone biochanin A, which has anticancer properties. Additionally, it was shown that biochanin A inhibited the activity of the aromatase enzyme and lowered mRNA expression in SK-BR3 cells, which are ER-negative breast cancer cells. According to Bhushan et al., biochanin A reduced the expression and activity of invasive enzymes, signalling pathways, and cell survival in cancer cells. In a different investigation, biochanin A was found to be effective at 5 or 15 mg/kg per day in diminishing the development of estrogen-dependent tumours in a xenograft mouse model by Moon et al.[15,16]

Our findings imply that temozolomide's anticancer effect on glioblastoma cells may be enhanced by the combination of temozolomide and biochanin A. These results add to our understanding of the ways in which biochanin A can be used to develop novel, highly active combination treatments.[17,18]

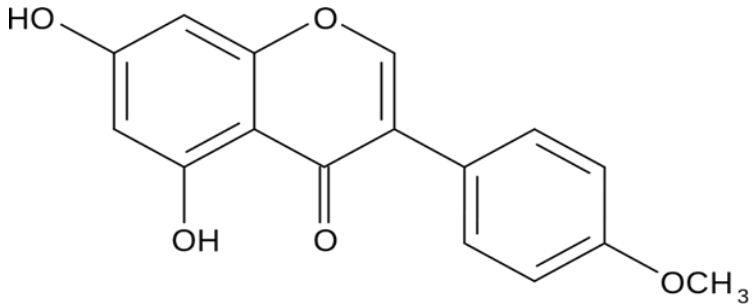

Figure 3. Biochanin A

3. Curcumin*:* Turmeric contains a polyphenolic molecule called curcumin, which has anti- breast cancer qualities in addition to a broad variety of other medical uses. Curcumin is recognised by cause apoptosis in breast cancer via altering the appearance of genes and proteins linked to apoptosis. According to recent research, curcumin can cause breast cancer cells to undergo apoptosis by raising the p53 level.[19,20] Curcumin has antiproliferative effects on cells by reducing NF-*κ*B expression. According to a different study, curcumin can inhibit urokinase type plasminogen activator protein expression via activating NF-κB, which eventually prevent MCF-7 cells from adhering and becoming invasive and slow the metastatic spread of breast cancer. Numerous studies have examined and assessed curcumin's impact on NF-*κ*B signalling; further research may be found by searching for this topic. According to Kakarala et al., curcumin inhibited Wnt signalling in MCF7 cells, a pathway that is essential to the rejuvenation of oneself of breast stem cells but is insensitive to changes in breast cancer. Curcumin has demonstrated great promise as a medication for the treatment of breast cancer by blocking this pathway.[21,22] Curcumin suppresses Bcl-2 expression by enhancing specific miRNAs linked to

the development of cancer. Tetrahydro curcumin's inhibitory activity on ATP-binding cassette (ABC)

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drug transporters. The development of a therapeutic action is hampered by curcumin's limited bioavailability, on the other hand. In order to address the drawback of curcumin's low bioavailability, future research should concentrate on creating stronger analogues of the compound. Liu and Chen (2013) investigated the effects of curcumin and discovered that the substance alters a number of molecular targets. It was recently shown that curcumin increased the expression of caspase-3 and caspase-9, which in turn caused apoptosis in MCF-7 cells.[23,24]

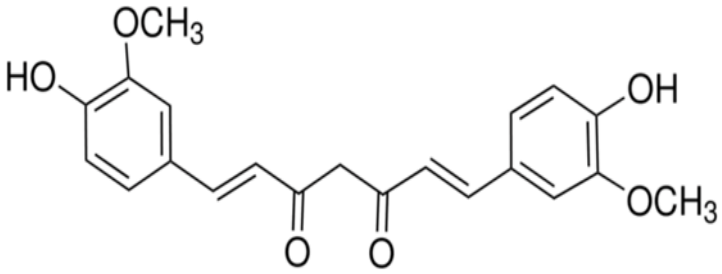

Figure 4. Curcumin

4. ***Epigallocatechin Gallate***. Green tea contains the highest concentration of phenolic catechins, epigallocatechin gallate, which is widely recognised for its health advantages.[25,26] According to a 2015 study by Deb et al., treating breast cancer cells with EGCG may cause the epigenetically suppressed TIMP-3 gene to become expressed. Class IHDACs and EZH2 protein levels were shown to drastically decline following EGCG treatment. EGCG also induces apoptosis through ER-independent mechanisms, such as the suppression of genes controlled by aryl hydrocarbons (AhRs).[27,28] The antiproliferative mechanism of EGCG was recently revealed by Baker and Bauer, who found that it did so by inhibiting the ERβ-specific inhibitor PHTPP. Moreover, EGCG has been shown to change EGFR activity and cause apoptosis in ER negative. It is also proposed that EGCG upregulates the expression of proapoptotic genes. It also upregulates the protein expression of p21 and plc. Furthermore, EGCG may enhance ionising radiation sensitivity and provide protection against the harmful side effects of radiation and chemotherapy, according to evidence from clinical trial-based research on breast cancer.[29,30]

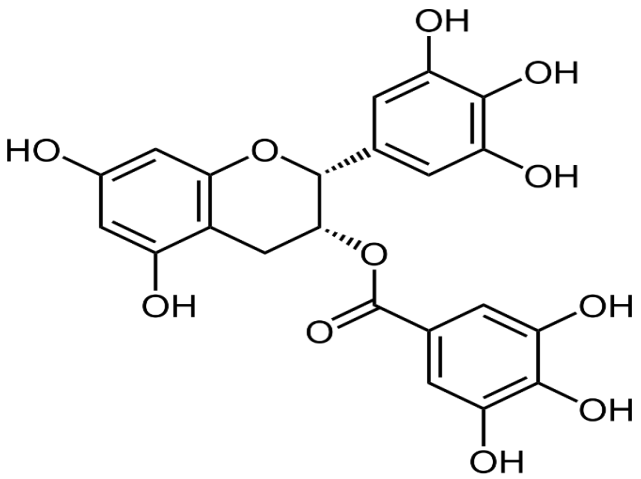

Figure 5. Epigallocatechin gallate

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JCHR (2024) 14(2), 3485-3505 | ISSN:2251-6727

5. ***Lycopene****:* Tight red carotene pigment Lycopene belongs to the tetraterpenoids family. It regulates a number of genes at play in apoptosis, implicated genes, and DNA repair in breast cancer cells.[31,32] Lycopene therapy had no impact on other genes' expression. Lycopene has the ability to cause cell death and have anticancer effects by altering cell growth factor signalling pathways and producing cell cycle arrest.[33,34] Therefore, further investigation is required to comprehend the role that lycopene plays as a chemo preventive agent in various pathways and subtypes of breast cancer. There aren't many studies on the benefits of lycopene by itself for health, so further halted the growth of triple-negative breast cancer cells by obstructing the downstream pathway that activates Akt.[35,36]

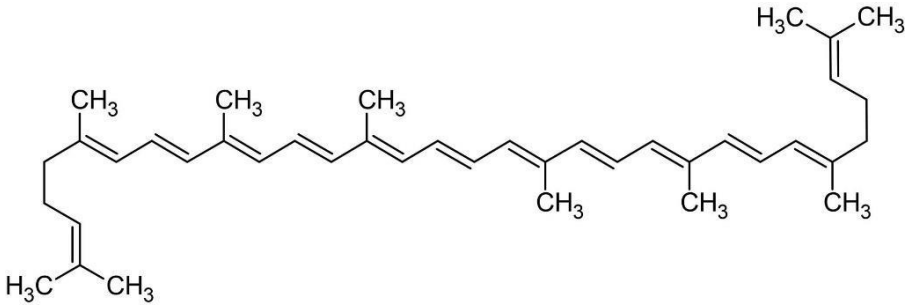

Figure 6. Lycopene

6. ***Shikonin****:* Shikonin is a substance that is mostly derived from the root extract of Lithospermum erythrorhizon. It demonstrated to have biological properties.[38,39] The Yao group reported that shikonin activated the Nrf2 pathway to decrease pS2. Shikonin suppressing the expression of genes that code for steroid sulfatase. During apoptosis stimulation, Shikonin targets multiple pathways, such as caspase-3 activation, suppression of the NF-B pathway, and modification of the apoptosis-related genes Bax and Bcl-2. Shikonin inhibits p65 and decreases IB phosphorylation to impede the NF-B pathway.[40,41] Shikonin changed matrix metalloproteinase-9, which decreased BrCa cell migration and invasion.[42,43] In vivo pharmacokinetics studies have demonstrated the reduced risk associated with shikonin, and it may be investigated further in trials aimed at treating breast cancer. Further investigation is required to improve shikonin's bioavailability profile, as it experiences high first-pass metabolism. [44,45]

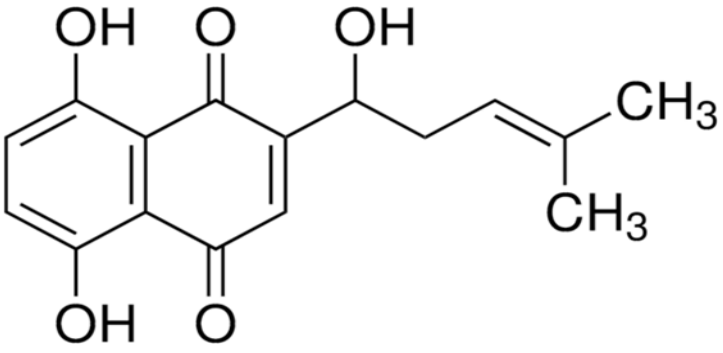

Figure7. Shikonin

7. ***Sulforaphane****:* It has been shown that the isothiocyanate sulforaphane (SFN), inhibits the growth, angiogenesis, and metastasis of cancer cells. In BrCa cells, it can result in both apoptosis and cell cycle arrest. [46,47] Following SFN therapy, In cancer cell lines, the nuclear factor kappa B signalling pathway was downregulated.[48,49] Kim et al. report that

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SFN decreased Bcl-2 expression and phosphorylated Akt serine/threonine kinase. One study found that SFN increases BrCa cells' chemosensitivity to paclitaxel. SFN also modifies the epigenetic expression of the hTERT and ER genes.[50,51] Li et al. found that SFN therapy decreased the population of ALDH+ cells in human BrCa cell lines as well as the number and size of mammospheres. Additionally, this study discovered that SFN significantly altered the exosomal secretion of DCIS, making them more akin to cancer cells that are not stem.[52,53] These studies demonstrate that SFN is capable of reprogramming cancer stem cells (CSCs) and eliminating them. SFN's absolute bioavailability dropped with increasing dosage, even though it is highly accepted, doesn't obvious harmful in humans, and it could even reach advantageous levels in plasma and tissue. Consequently, sulforaphane may prove to be a useful chemotherapeutic therapy adjuvant. This is especially true since the majority of medications are unable to eradicate CSCs, which might result in tumour resistance and recurrence. More research is required to confirm the course of therapy and efficacy of SFN on modulating chemo preventive therapy, particularly large population-based studies.[54,55]

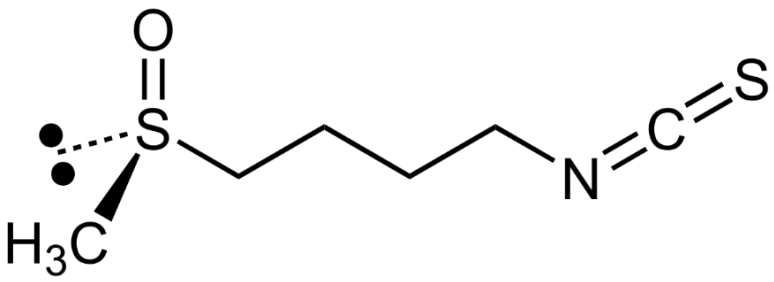

Figure 8. Sulforaphane

8. Silibinin: Flavonolignan has been demonstrated to cause breast cancer cells to undergo autophagic cell death upregulation of Atg12-Atg5 formation, reduction in the expression of Bcl-2, and enhancement of beclin-1 expression.[56,57] Silibinin's anticancer properties include suppressing Wnt/LRP6 signalling and downregulating TPA-induced MMP-9 expression via blocking COX-2 expression in breast cancer cells. Silibinin has been shown to both sensitise chemo resistant breast cancer cells and boost the effectiveness of paclitaxel and cisplatin.[58,59] It is the primary active ingredient in the silymarin complex that is derived from Silybum marianum and exhibits strong hepatoprotective properties. By inhibiting CXCR4, the substance also shown anticancer qualities and stopped breast cancer cells from metastasizing (chemokine receptor type 4).[60,61] It is the primary active ingredient in the silymarin complex that is derived from Silybum marianum and exhibits strong hepatoprotective properties. [62,63] By inhibiting CXCR4, the substance also shown anticancer qualities and stopped breast cancer cells from metastasizing.[64,65] Through suppression of the major oncogenic pathways and paclitaxel-resistant cells at 400 mM concentration, silibinin also sensitised resistant breast cancer cells to doxorubicin and paclitaxel.[66,67] Similarly, via downregulating cyclin D1 and hTERT, silibinin and chrysin.[68,69] Jahanafrooz et al., however, demonstrated that other pathways are in charge of miR-21's anti-apoptotic action and that down-regulating it in response to silibinin therapy had little influence on the protein's antitumorigenic ability in breast cancer cells. [70,71] Silibinin caused ROS-dependent mitochondrial dysfunction (DJm) and a decrease in ATP levels via BNIP3 to cause autophagic cell death in MCF-7 cells.[72,73] Nevertheless, Zheng et al. (2015) claim that down-regulating ERa expression and the ensuing suppression of the ERK and mTOR signalling pathways are the causes of silibinin's anti-apoptotic and autophagy.[74,75]

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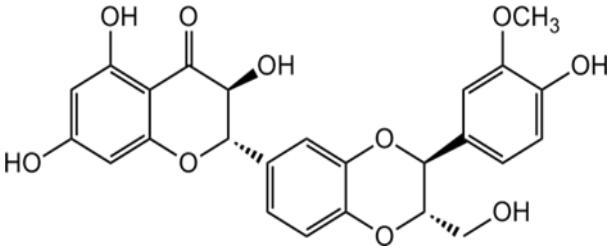

Figure 9. Silibinin

9. Quercetin: Leptin is a novel target in breast cancer therapy because quercetin, a well- researched and potentially chemopreventive chemical found in many plant foods, inhibited thedevelopment of T47D cells by suppressing leptin gene expression and secretion.[76,77] Nec-1, an inhibitor of necroptosis, was shown to improve the proliferation and viability of MCF-7 cells while decreasing the expression of Bax and the apoptotic index, indicating that necroptosis is the primary cause of death. Similarly, the substance inhibited Twist via the p38MAPK pathway, exhibiting apoptotic activity in MCF-7 cells.[78,79] Similarly, it was also observed that MCF-7 cells exhibited anti-proliferative and apoptotic activities through Go/G1-phase arrest and decreased survivin expression. Combining Quercetin with ascorbic acid (vitamin C) in combination with prescription drugs like doxorubicin or paclitaxel significantly improved the anti-cancer activities of the treatments in breast cancer cells by reducing the S and Go/G1 phases. Quercetin reduced tamoxifen resistance in cells by downregulating.[80,81] In contrast, AU565 cells experience G2/M-phase arrest and apoptosis due to lowered Her-2 expression. Through the modulation of EMT markers, quercetin demonstrated anti-metastatic properties in TNBC cells.[82,83] It changed the nuclear location of b-catenin and modulated the target genes of b-catenin, cyclin, resulting in a mesenchymal-to-epithelial transition mediated by an increase in E-cadherin and a decrease in vimentin. Quercetin suppressed the calcineurin/NFAT pathway. The substance also caused mitochondrial-mediated apoptosis and suppressed EGFR to prevent invasion.[84,85]

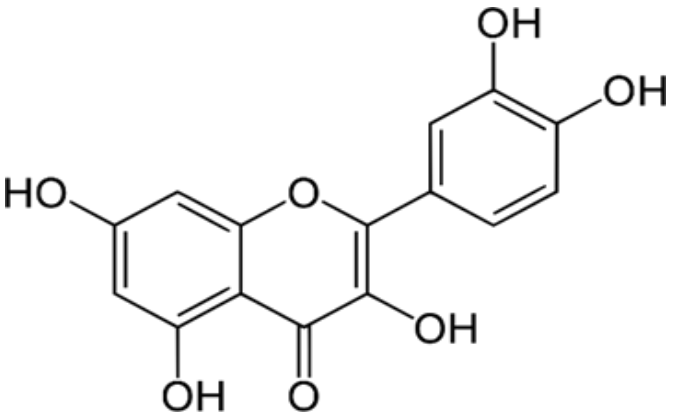

Figure 10. Quercetin

10. Thymoquinone: Black seed oil's thymoquinone (TQ), an anti-inflammatory, antioxidant, carcinogenic, and cytotoxic component, has also been studied in relation to breast cancer treatment. In ER positive (MCF-7) cells, the chemical caused apoptosis-related genes to express differently. The p38-MAPK and MAPK pathways were inhibited as a result of the PTPRR gene being upregulated. The intrinsic apoptotic pathway is implicated, as evidenced by the up-regulation of TP53 and the down-regulation of Bcl-2 that was caused by inhibition of p38-MAPK. Moreover, downregulation of the CARD16 gene demonstrated caspase's involvement in apoptosis.[86,87] TQ's impact on the miRNA profile and molecular mechanism was recently emphasised utilising MCF-7 cells, and it was

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discovered that the compound's primary targets. When radiation-induced breast cancer metastasized, TQ pre-sensitization restored the expression of epithelial markers like as cytokeratin 19 and E-cadherin, as well as mesenchymal markers including integrin-aV, MMP-2, and MMP-9, and TGF-b.[88,89] TQ also reduced the activity of global histone deacetylase, which had an anticancer effect on breast cancer cells (HDAC). The substance caused G2/M phase arrest, reactivated the HDAC target genes p21 and mastin, lowered Bcl-2, and elevated Bax. Together, TQ and tamoxifen reduced cell viability and caused apoptosis in both estrogen-positive (MCF-7) and estrogen-negative cell lines.[90,91] Through a number of cascades including tumour suppressor genes, p53 signalling, and extrinsic apoptosis, the chemical made breast cancer cells more sensitive to paclitaxel. Furthermore, TQ increased the expression of tumour suppressor genes such as BRCA1, p21, and Hic1 and controlled apoptosis-inducible genes via death receptors. Furthermore, large dosages of TQ increased growth hormones like VEGF and EGF and downregulated pro-apoptotic proteins like caspases. Similarly, concurrent administration of melatonin and thymoquinone significantly reduced the growth of the tumour by stimulating apoptosis, triggering the Th1 immune response, and preventing angiogenesis.[92,93]

Thymoquinone is found in Nigella sativa seeds, which are cultivated in Western Asian and Mediterranean regions (TQ). It has been demonstrated that this substance is resistant to leukaemia, osteosarcoma, breast cancer, ovarian cancer, liver cancer, and colorectal cancer as well as myeloblastic pancreatic adenocarcinoma. The anticancer impact of TQ involves multiple proteins.[94,95] In cancer cells, TQ enhances pro-apoptotic protein levels while lowering anti-apoptotic protein levels, suggesting antiproliferative properties.[96,97] Reduced levels of anti-apoptotic proteins, elevated p38 phosphorylation, and a decline in breast tumours indicate that TQ is an effective treatment for breast cancer. TQ has the ability to lower cell production as well as block S phase molecules and induce sub-G1 arrest in cells. TQ causes apoptosis via controlling a number of p53-dependent and p53-independent targets. By targeting NF-ɹB and changing the cell cycle, TQ inhibits the formation of tumours and the proliferation of cells. Following long-term therapy, even modest concentrations of BrCa cells are inhibited. Poly (ADP-ribose) polymerase breaks down in response to TQ, while H2AX rises, Akt phosphorylation falls, and X-linked inhibitor of apoptosis decreases.[98,99] Moreover, it functions as a PPAR ligand, preventing BrCa MCF-7/DOX cell proliferation. TQ increases the presence of PTEN protein while decreasing Akt phosphorylation. By preventing Akt phosphorylation, which is necessary for cell survival, TQ stops cells from growing. In cells, TQ inhibits them during the G2/M phase. By reducing the synthesis of cyclin D1 and cyclin E and phosphorylating, TQ inhibits Akt. Consequently, TQ induces apoptosis in BrCa cells, making it an effective treatment for the illness.[100,101]

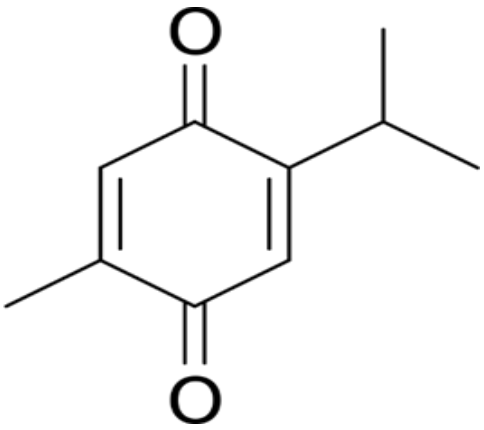

Figure 11. Thymoquinone

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11. Benzyl isothiocyanate: An isothiocyanate found in cruciferous vegetables called benzoyl isothiocyanate has anti-carcinogenic properties. By changing the dynamics of the mitochondria, BITC caused breast cancer cells to undergo apoptosis. The substance significantly decreased the amounts of fusion proteins in breast cancer cells, indicating that it is detrimental to the fusion machinery and purpose of mitochondrial dynamics.[102,103] BITC inhibited the development of p53-mutant cells by activating the p53-signalling network. The substance caused p73 to become expressed in these mutant cells, breaking the connection between mutant-p53 and p73. This allowed p73 to be released from sequestration and resume its transcriptional activity. Liver kinase, A suppressor of tumours, was discovered to represent a crucial molecular mechanism underpinning the compound's anti-cancer action. LKB1 was transcriptionally increased by p73 and p53 in breast cancer cells with mutant p53 and wild- type p53, respectively. Moreover, it was demonstrated that LKB1 recruits into p53-responsivegene promoters via tethering with a feed-forward manner.[104,105] By lowering p-Akt and uPA activity, BITC also prevented MDA-MB-231 cells from migrating and invading. It was also discovered that sfRON, or truncated receptor d'origine nantais, is a novel molecular target for apoptosis induction in breast cancer cells. Through the regulation of sf RON, BITC promoted apoptosis in cells. In these cells, overexpression of sf RON increased apoptosis independently of JNK or MAPK hyperphosphorylation.[106,107] Furthermore, after BITC treatment, activation of Bak and Bax in sf RON overexpressing cells was significantly increased, although G2/M phase arrest and ROS production were reduced.[108,109]

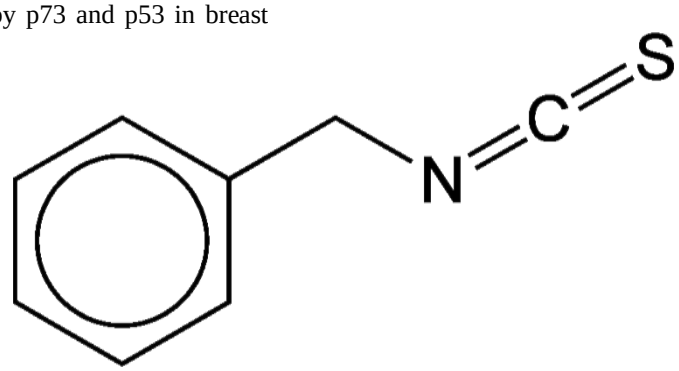

Figure 12. Benzyl isothiocyanate

12. Apigenin: The well-known anti-inflammatory flavonoid apigenin, which is found in parsley and many other plants, inhibited TNFa-mediated chemokine production in TNBC cells.[110,111] IKBKe signalling was suppressed in order for apigenin to inhibit CCL2. Apigenin inhibited drug resistance by downregulating MDR1 and Pglycoprotein, suppressing STAT3 signalling and subsequent nuclear translocation, and reducing colonisation and cell proliferation in adriamycin-resistant MCF-7 cells. Additionally, the chemical reduced the STAT3 target genes MMP-9 and VEGF's release in these cells.[112,113] The compound inhibited phospho-STAT3, phospho-JAK1, and phospho-JAK2 in HER2-expressing breast cancer cells, preventing CoCl2-induced VEGF production and STAT3 nuclear translocation..[114,115] The same scientists previously stated that apigenin inhibits NF-kB and STAT3 and induces p53 in HER2-overexpressing MCF-7 cells, hence inducing apoptosis via an extrinsic mechanism.[116,117] Moreover, apigenin boosted p21WAF1/CIP1 and its association with nuclear antigen of proliferating cells, preventing the advancement of the cell cycle. Additionally, it was shown that acetylated histone H3 increased and that histone deacetylase activity was inhibited.[118,119]

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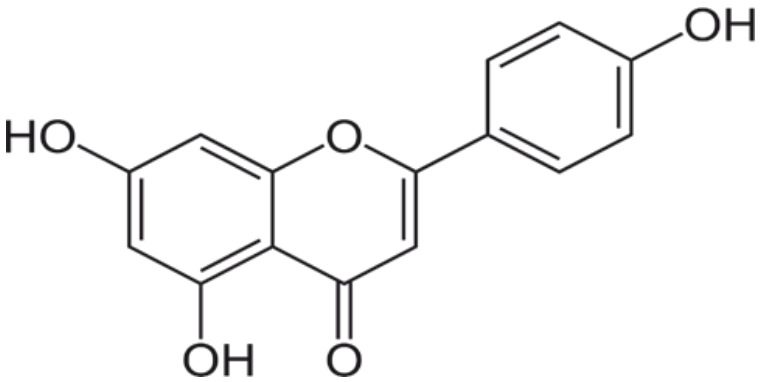
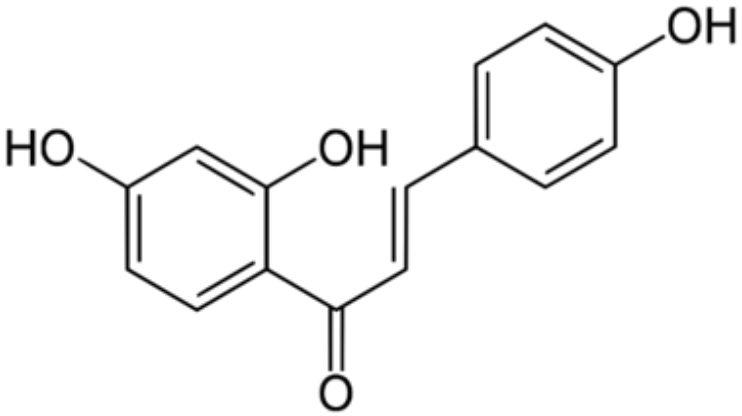


Figure 13. Apigenin

13. **Isoliquiritigenin**: Moreover, apigenin boosted p21WAF1/CIP1 and its association with nuclear antigen of proliferating cells, preventing the advancement of the cell cycle. Additionally, it was shown that acetylated histone H3 increased and that histone deacetylase activity was inhibited. The substance also lowered p-Akt.[120,121] According to Peng et al. (2017), ISL downregulates miR-374a, causing apoptosis and preventing metastasis in breast cancercells. Reduced miR-374a expression raised PTEN expression, which stopped aberrant Akt signalling.[122,123] Additionally, the chemical inhibited the invasion of breast cancer cells by downregulating miR-21 and upregulating the tumour suppressor gene RECK.[124,125] Furthermore, ISL promoted autophagy, chemosensitized, and stopped the cell cycle in MCF-7/ADR cells. It also accelerated the lysosome-autophagy pathway's ability to degrade ABCG2. ULK1 expression was upregulated as a result of suppression of miR-25, which was linked to autophagy induction (a kinase involved in autophagy).[126,127] Breast cancer cell migration was prevented by ISL therapy due to its inhibition. This resulted in decreased expressions of MMP-2, MMP-9, VEGF, and HIF-1a. 48 ISL inhibited bCSCs to stop mammary carcinogenesis and promoted the demethylation of the WIF1 promoter by docking into the DNMT1 catalytic domain. This increased the expression of the WIF1 gene.[128,129] Additionally, the chemical chemosensitized bCSCs by blocking the b-catenin/ABCG2 signalling pathway by docking into the immunoglobulin protein-binding ATP domain of GRP78. This inhibited the protein's ATPase function, which led to its separation from b-catenin.[130]



14.

Figure 14. Isoliquiritigenin

15. Ginsenosides: The primary pharmacologically active saponins found in ginseng root, known as ginsenosides, are widely recognised for their potentially restorative and healing properties.[131,132] Ginsenoside Rh2 enhanced immunogenicity and suppressed MCF-7 cell development by inducing epigenetic methylation changes in genes linked to immunity and carcinogenesis. Genes with low

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methylation, such as C1orf198, ST3GAL4, and CLINT1, showed upregulation, whereas genes with high methylation, such as INSL5, OR52A1, and CASP1, showed downregulation. Furthermore, hypomethylation at particular CpGs was also seen in LINE1, a global methylation marker.[133,134] Additionally, Rh2 reversed the effects of docetaxel or adriamycin resistance in MCF-7 cells that were resistant by expressing different microRNAs. In TNBC cells, ginsenoside Rg3 increased the cytotoxic effect of paclitaxel by upregulating caspase-3 and Bax and inhibiting NF-kB and Bcl-2.[135,136] Rg3-caused breast cancer cells to undergo apoptosis is also caused by suppression of NF-kB through Akt and ERK inactivation, according to a paper by Kim et al. (2014). Rg3 and recombinant human endostar together slowed the growth of breast cancer, prevented angiogenesis and cell invasion, and enhanced autophagy by lowering the amounts of the genes.[137,138] In a similar vein, ginsenoside Rg5 inhibited the growth of breast cancer via raising AMPK activation and subsequently lowering S6 and p70S6K activation. In breast cancer cell lines, the chemical upregulated and downregulated.[139,140]

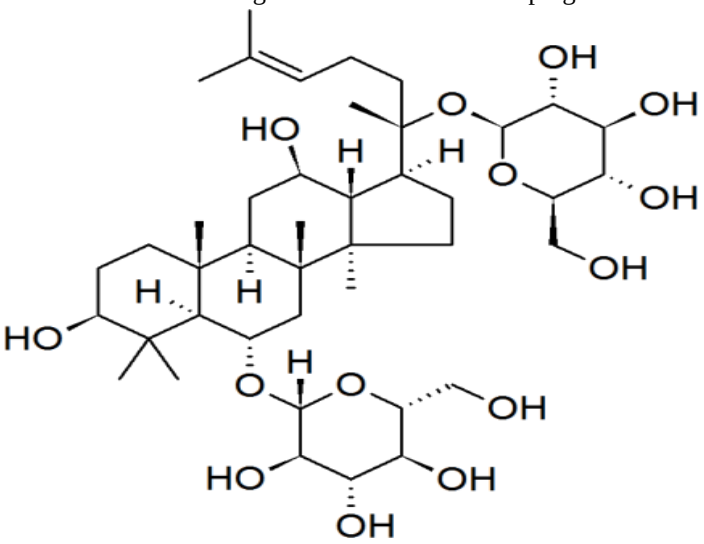

Figure 15. Ginsenosides

16. Tetrandrine: Tetrandrine has antiproliferative qualities and prevents the growth of cancercells. The alkaloid known as dibenzyl tetrahydro isoquinoline was found in the Asian medicinal herb Stephania tetrandra (Chinese plant). It has been demonstrated that this naturally occurring chemical can cause apoptosis in breast cancers, leukaemia, melanomas, and prostate malignancies.[141,142] This medication affects tumour cell resistance and can help human BrCa cells overcome their drug resistance, making it useful for treating a range of malignancies. Additionally, tetrandrine promotes autophagy.[143,144] This medication decreases the production of the aldehyde dehydrogenase protein and the formation of mammospheres, a sign of the proliferation of cancer cells. Moreover, downregulating aldehyde dehydrogenase proteins has antiproliferative effects since they are linked to the proliferation of BrCa cells.[145,146] Consequently, tetrandrine possesses the capacity to efficiently cause cancer cells to die, and these properties make it a potentially viable treatment for the suppression and treatment of breast cancer.[147,148] Tetrandrine has been demonstrated to be a checkpoint inhibitor of the cancer cell cycle, which can stop cell division. [149,150] Like the soybean isoflavone daidzein metabolite 30,40,7-trihydroxyisoflavone, tecandrin inhibits the ATP binding site of CDKs, suppressing. It also stops cells from going through the G1–S phase. [151]

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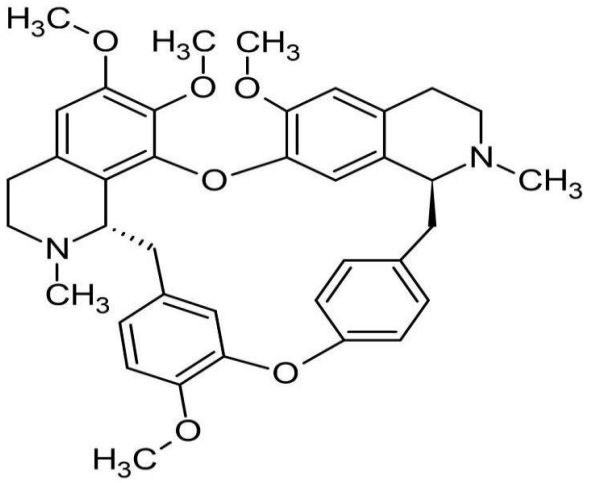

Figure 16. Tetrandrine

3. Challenges in the Management of Breast Cancer

Advancements in breast cancer treatment have led to improvements but also introduced new challenges and complexities in management.

Cost and Accessibility: Financial barriers, such as cost or insurance limitations, may hinder access to advanced breast cancer treatments for some patients, perpetuating disparities in healthcare access and potentially impacting treatment outcomes and quality of care.[152,153] **Ethical and Social Implications:** The increasing utilisation of personalised medicine and genomic testing in the management of breast cancer may give rise to ethical and social concerns, including genetic privacy, discrimination on the basis of genetic information, and possible psychological fallout from being aware of one's genetic susceptibility to breast cancer. These difficulties necessitate a thorough evaluation of the moral and societal implications in order to safeguard the welfare and rights of patients.

Integration and Implementation: It can be difficult and complex to incorporate new technologies and therapies into standard clinical practise. The adoption of new technology by healthcare practitioners may present logistical hurdles in terms of infrastructure, training, and equipment requirements, as well as a learning curve.[154,155]

Evidence-based Decision Making: New treatment options for breast cancer have been made possible by medical developments, but there may not be enough information to determine if they are safe and effective over the long term. This can make it difficult for patients and healthcare professionals to decide on the best course of action, especially in quickly developing disciplines like immunotherapy and targeted medicines.

Patient Education and Informed Consent: As the treatment of breast cancer becomes more sophisticated, patient education and informed consent become essential. With technology advancing so quickly, it can be difficult to ensure sure patients have enough information to make educated decisions. Patients need to be aware of the dangers, advantages, restrictions, and potential ramifications of various treatment options, including customised medicine and genetic testing.

Health Disparities: There might be differences in access to these technologies even with the advancements in breast cancer care, especially for minority and underserved groups. It is still necessary to pay attention to and take action in order to address health inequities and provide fair access to improvements in breast cancer treatment.[156,157]

4. Future Prospect of Herbal Management

Currently, a number of obstacles, primarily related to the toxic side effects and medication resistance, are interfering with the traditional therapy options used in the treatment of breast cancer. Patients are experiencing a variety of unavoidable side effects from radiation or chemotherapy. Once more, the poor responses to this therapy are caused by drug resistance. Since they can work in concert with many

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chemotherapy drugs and increase their efficacy, natural chemicals derived from food sources can be a godsend in this situation.[158,159] When combined with additional medications, a variety of natural chemicals are said to have very beneficial results in the treatment of breast cancer. This analysis is centred on a few natural substances that have the ability to significantly alter any breast cancer-related pathway. Nonetheless, certain substances have many mechanisms of action. They are therefore able to demonstrate a higher level of efficacy. Once more, a few of these substances may exhibit synergistic effects or combat multidrug resistance. Taking into account each of these aspects, it can be concluded that, with more thorough research, natural substances may prove to be highly promising in the near future in order to cure and prevent breast cancer.[160,161]

5. Conclusion

It is impossible to deny the importance and role that naturally occurring chemicals play in themanagement and prophylaxis of breast cancer. Natural food compounds have a wide range of applications and having been employed as a very lengthy period in conventional medicine. Research efforts to maximise the action of these molecules and develop them as therapeutics to treat breast cancer patients need to be prioritised more. Due to their capacity to alter several pathways, these natural chemicals have the potential to both function as a therapy system on their own and enhance the efficacy of other conventional therapies.[162,163] In addition, they have a significant impact on preventing breast cancer. They have the ability to operate through several pathways without causing any unique or harmful effects. This work highlights several natural chemicals and discusses their mechanism of action, route, synergistic activity, and future potential. Therefore, more thorough research is needed to establish these compounds' suitable role, which will help us better understand how to employ them therapeutically and combat the current issues associated with breast cancer.[164,165]

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Journal of Chemical Health Risks
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JCHR (2024) 14(2), 3485-3505 | ISSN:2251-6727

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