therapeutics

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Review

How Natural Therapies Can Combat Neoplastic Disease by Targeting Key Survival Mechanisms and Signaling Pathways

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Abstract: Plant extracts are increasingly becoming an answer to expensive, high-dose, synthesized chemotherapy, with milder side effects and easier accessibility. Many botanical plants contain active ingredients, such as terpenoids and alkaloids, which may combat cancer; however, studies need to be performed to test whether they are solely effective enough and whether the extracted compounds are selective for the tumor itself. Many chemotherapy drugs were initially of botanical origin, such as vincristine from Catharanthus roseus and paclitaxel from the Taxus baccata tree. The objective of this review is to assess the mechanisms of herbal therapeutics in their role against malignancy. Ajwa, curcumin, ginseng, lycopene, and ursolic acid were all respectively evaluated in the paper for their prevalent properties, their method of extraction, notable usage in medicine, which pathways they activate, and whether the transductions can disrupt cancer formation or proliferation. The findings from the review demonstrated that all the therapeutics exhibited pro-apoptotic behavior, Ajwa and curcumin exerted cell cycle arrest upon neoplasms, and Ajwa, curcumin, and lycopene showed anti-metastatic behavior. Most extracts were tested on colorectal cancer, and the pathways most commonly applied were through BAX/Bcl2 and endoproteases, such as caspase-3 and caspase-9, indicating predominantly mitochondrial apoptosis. In addition, cell cycle arrest was noted to occur during the G2/M phase via Wnt/β-catenin in both curcumin and ginseng, independently of the Wnt/β-catenin pathway in Ajwa constituents, reducing cell viability. All of these studies were demonstrated in vitro within varieties of single cell cultures, which did not take into account bioavailability nor properly demonstrate the tumor microenvironment, which may not yield the same results in vivo. Clinical trials need to be undergone to appropriately test effective dosages, as if a compound is strongly pro-apoptotic, it may not be selective just to tumor cells but also to healthy cells, which may impair their functions.

Keywords: natural compounds; cancer therapy; tumorigenesis; plant therapy; cancer signaling

Academic Editor: Greta Varchi

Received: 27 July 2024
Revised: 15 November 2024
Accepted: 24 February 2025
Published: 5 March 2025

Citation: Karagil, S.; Szczesnowska, A.; Haddad, N.; Magura Gamaethige, S.; Coakley, E.; Dawood, N.; Rama, V.J.; Barker, J.; Langat, M.K.; Morgan, H.; et al. How Natural Therapies Can Combat Neoplastic Disease by Targeting Key Survival Mechanisms and Signaling Pathways. *Therapeutics* **2025**, 2, 5. https://doi.org/10.3390/therapeutics2010005

1. Introduction to Natural Therapies

Therapies using natural products have recently become a source of interest in research due to their availability, low cost, and minimal side effects in comparison to current invasive treatments for neoplastic diseases, for example. Natural therapies can take the form of edible foods or extracts of certain active components with pharmaceutical and medicinal properties. The potential benefits of these therapies are more pronounced in developed countries, as they provide a cost-effective and easily accessible source of potential treatment and/or management of both chronic and severe diseases. This review will focus on natural therapies in the context of one of the most abundant diseases in the world: cancer. To consider the scale of how many people are affected by cancer, it was the first or second leading cause of death in under 70s in most countries in 2019, with a confirmation of 19.3 million new cancer cases in 2020 [1]. The mortality rate in developing countries due to low economic levels and lack of proper healthcare makes the findings of this review even more crucial in the discovery of natural compounds to help combat this debilitating disease.

2. Effect of Natural Therapies on Disease

2.1. Ajwa Date Variety and Cancer

The date fruit (*Phoenix dactylifera* L.) is one of the mostly utilized native fruits specifically grown in the city of Al-Madinah Al-Munawara, in the Kingdom of Saudi Arabia (KSA) [2,3]. The Ajwa date variety, belonging to the *Arecaceae* family, has been described as a traditional and alternative medicine for providing various health benefits [4–6]. It has a high nutritional value and is rich in dietary fibers, carbohydrates, proteins, minerals, and fats [5,7]. It also contains a range of phytochemicals, such as phytosterols, polyphenols, flavonoids, and glycosides. These phytochemicals have anti-inflammatory, antioxidant, cardioprotective, hypolipidemic, and anticancer properties [3,7]. Bioactive compounds existing in the Ajwa date fruit have been found to have the potential to prevent cellular damage and to work as a cancer therapeutic [6]. The phenolic compounds present have a strong effect in eliminating free radicals and can restrict the progression and development of cancer [8]. Recently conducted studies have elucidated the importance of the Ajwa date in various cancer types, including breast cancer, colorectal cancer (adenocarcinoma), hepatocellular carcinoma, and prostate cancer. The growth and proliferation of colon cancer (CaCo2) cells in vitro were shown to be inhibited by polyphenols [2]. Prostate cancer in PC3 cells treated with an ethyl acetate fraction of the Ajwa date (EAFAD) indicated a strong anti-proliferative activity, e.g., cell shrinkage, loss of cytoskeletal structure, and DNA fragmentation in both a concentrated and time-dependent manner [7,9]. Treatment of cells with EAFAD reduced the potential of cells to metastasize in cancer, and this resulted in cancer cells undergoing numerous morphological changes, such as chromatin condensation and degradation of the nuclei, which are indications of apoptosis. The anti-cancer property of the Ajwa date has also been analyzed in MCF7 (human breast adenocarcinoma) and hepatocellular carcinoma in HEPG2 cell lines through effects on apoptosis and cell cycle arrest [4].

Expanding further upon the findings in HEPG2 cells, the ethanolic extract of Ajwa date pulp induced apoptosis in both a dose- and time-dependent manner. Cells treated with a high dose of Ajwa date extract prompted cells to enter into late-stage apoptosis. The intracellular ROS production of HCC (hepatocellular carcinoma) cells was stimulated by the treatment of Ajwa date extract, leading to an increase in oxidative stress, which, in turn, caused the disruption of the cellular cytoskeleton and a decrease in mitochondrial membrane potential, inducing apoptotic cell death. Proliferation of HCC cells was also reduced upon treatment with Ajwa extract through cell cycle arrest in the S and G2/M phases [3]. Recently, human breast cancer adenocarcinoma (MCF7) cells were found to be

inhibited by the methanol extract of the Ajwa date by causing an increase in the proportion of cells in the late apoptotic stage and cell cycle inhibition in a dose- and time-dependent manner, similar to what was seen in HEPG2 cells [2,3]. The methanolic extract of the Ajwa date (MEAD) induced contraction and fragmentation of cells and loss in the adherence of cells, causing apoptosis and anoikis. MCF7 cell proliferation was inhibited in vitro with cell cycle arrest in the S phase of mitosis. Moreover, MCF7 cell death with the treatment of MEAD was due to activation by p53-mediated signaling. MEAD induced the transcriptional activity of pro-apoptotic genes Bax/Bcl2 and decreased the anti-apoptotic gene Bcl-2 through the p53-mediated signaling pathway, leading to apoptotic cell death [5]. Ajwa date extract has also been studied against human triple-negative breast cancer (MDA-MB-231) cells. Ethanolic Ajwa date pulp extract (ADPE) was also shown to induce apoptosis in the same way as other cancer types by causing an alteration in cellular morphology, ROS production, and the cell cycle. ADPE also led to the upregulation of p53, Bax, and cleaved caspases, which, in turn, downregulated the Bcl-2 and AKT/mTOR pathways. Suppression of the AKT/mTOR pathway resulted in a loss of the cells' ability to survive and proliferate [6]. The use of Ajwa date extracts was found to be non-toxic and to exert anticancer properties in different cancer types by inhibiting cell proliferation and inducing apoptotic cell death. They could thus be a novel and potent natural anticancer treatment in the future, with minimal side effects in comparison to current first-line treatments, which result in a wide range of debilitating side effects [8,10].

2.2. Curcumin and Cancer

Curcumin originated from the rhizomes of *Curcuma longa* (turmeric), a yellow-colored, lipophilic, polyphenol compound that has been traditionally used and valued in Asian countries due to its pharmacological properties against several pathophysiological conditions [11–13]. Several studies have shown that curcumin has been effective as an anti-inflammatory, antioxidant, cardioprotective, and anticancer agent [14,15]. Curcumin has also gained increased attention in cancer prevention and/or treatment due to being safe, multi-cite targeted, non-toxic, reliable, and cost-effective [13,14]. The strong anticancer characteristics of curcumin has been validated against a wide range of human cancers, such as breast, colon, pancreatic, bladder, and prostate cancers [13,16,17]. Curcumin can inhibit the major stages of cancer progression, including proliferation, survival, invasion, metastasis, angiogenesis, and chemoresistance in various tumor cell lines [13,18]. The vital anticancer role of curcumin is primarily attributed to its interference with multiple cellular signaling cascades, including Wnt/β-catenin, PI3K/Akt/mTOR, JAK/STAT, MAPK, NFkB, VEGF, and p53, as well as various genes, like cyclin D1, TP53, BAX, BCL-2, and MMPs, which are known to modulate cellular growth, the cell cycle, and the apoptosis of tumors [16–19]. Curcumin inhibits the PI3K/Akt pathway, leading to an increase in radiation-induced apoptosis. Inactivation of Akt phosphorylation by curcumin downregulates anti-apoptotic genes Bcl-2 and Bcl-xl and upregulates pro-apoptotic genes Bax, p53, and p21, resulting in an increase in cytochrome C release and thus oxidative stress, inducing apoptosis of the cell [12,16,17,20]. Curcumin also plays a crucial role in the downregulation of COX-2 expression to suppress the progression of tumor cells [20]. Studies have demonstrated that curcumin exerts an anti-proliferative role via the inhibition of NFkB and the suppression of its downstream genes that are necessary for cell adhesion. Inhibition of NFkB by curcumin causes the downregulation of cyclin D1, which, in turn, prevents cell cycle progression [12,20,21]. Moreover, curcumin also reduces the potential of tumor cells to metastasize via modulating the matrix metalloproteins family (MMPs) members, such as MMP-2 and MMP-9. Downregulation of MMPs by curcumin provides an essential role in the management of cancer [16,17,20,21]. Curcumin was also found to inhibit the

proliferation of breast cancer cells through various mechanisms of action, which include cell cycle arrest, p53-dependent apoptosis, downregulation of transcription factors, and alterations in the expressions of signaling proteins [22]. Curcumin suppressed the proliferative activity of breast cancer cells through the inhibition of the Akt/mTOR pathway by inducing cell cycle arrest, as well as inducing apoptosis, via reduced Bcl-2, upregulated Bax, and cleaved caspase-3. Curcumin can also regulate the metastasis of breast cancer cells by inhibiting MMP-2 and MMP-9 via the downregulation of NFkB signaling pathways [20,22]. The effect of the anti-invasive activity of curcumin shown in MDA-MB-231 breast cancer cells through MMP-2 downregulation and a reduction in the weight of the tumor was observed in a dose-dependent manner [23,24]. In MCF-7 breast cancer cells, curcumin has been shown to arrest the cell cycle in the G2/M phase through Wnt/β-catenin pathways and to induce p53-dependent apoptosis [22,24]. Studies on the colon cancer cell line have shown a suppressed proliferation, which promoted autophagy in response to curcumin in a dose-dependent manner. In addition, expression of the Yes-associated protein (YAP) was suppressed in curcumin-treated colon cancer cells [18,25]. In prostate cancer, curcumin directly targets the PI3K/Akt pathway, and the inhibition of this pathway leads to radiation-induced apoptosis [12]. Curcumin's non-toxicity and tolerability can target numerous cancer hallmarks by modulating different targets to inhibit cell proliferation, invasion, and metastasis of cancer cells and induce apoptosis [13]. Therefore, curcumin has a great potential in becoming a novel drug in future anticancer therapies.

2.3. Ginseng and Cancer

Ginseng has been used extensively in traditional Chinese medicine [26] for a wide range of diseases. It is even mentioned in the Bencao Gangmu text of the Middle Ages as "yellow Shen", which was deemed a remedy for fever and digestive and cardiovascular issues. It also stimulates and modulates the immune system [27] through its variety of constituent ginsenosides, alkaloids, and gintonin, which have anti-inflammatory properties and are potentially adaptogens. Using Soxhlet extraction with aqueous 1-butanol at 120 °C for at least an hour helps extract ginseng, but the active compound concentration increases with longer extraction times [28].

There are three types of ginsenosides: Rb, Rg, and Ro. These are triterpenoid saponins which are the bioactive elements of the ginseng [28]. In neoplastic diseases, Rg5 induces apoptosis in HeLa (human cervical cancer cells) and MS751 (epidermoid carcinoma) cells by inducing fragmentation [29]. Rg3 ginsenoside reduces A549 and H1299 tumor cell proliferation [30], which could be due to its anti-angiogenic nature [9]. Harman is a ginseng alkaloid that exudes an antibacterial effect against *Vibrio anguillarum* [31] and is shown to be cytotoxic to PC12 (rat adrenal gland tumor) cells [32]. Gintonin is a lipoprotein that acts as a substrate for the lysophosphatidic acid receptor [33], which is associated with a functional nervous system. Gintonin plays a role in the prevention of neuronal degradation and decreasing the progression of Alzheimer's and Parkinson's diseases. Ginseng extract itself seems to work through the WNT pathway in the 528NS cancer cell line, which decreases cell viability. Rg3 and Rh2 ginsenosides are also responsible for a decreased proliferation rate in vitro [34]. A different ginsenoside, Rf, has anti-melanogenic properties by causing lowered expressions of the CREB (cAMP response element binding protein), MITF, and tyrosinases in B16BL6 melanoma cells [35] and the inhibition of the CREB/MITF pathway. Ginseng can reduce hay fever by blocking histamine responses by decreasing the expression of histamine receptor subtype 1 and the TRPV1 channel that stops the binding of histamines [36], as well as interleukins such as IL-1α, IL-8, and IL-10, which are also further involved with inflammation [37].

2.4. Lycopene and Cancer

Another natural product that could be influential in the treatment and/or management of diseases such as cancer is lycopene. Lycopene is an acyclic A-carotene responsible for the characteristic red pigmentation of ripe tomatoes and other fruits, such as watermelon and papaya [38]. Lycopene cannot be synthesized by the human body and therefore is obtained by humans via their diet, commonly from foods such as tomatoes, grapefruit, pink guava, pawpaw, and watermelon. Consumptions of these foods account for 85% of the lycopene in most diets [39]. In addition to this, lycopene is a potent antioxidant and scavenger of free radicals, exhibiting potential protective anti-cancer activities, which may reduce the risk of cancers, such as prostate, lung, and colon cancers [38].

The anti-cancer effects of lycopene have somewhat been proved by a variety of epidemiological studies, which have shown that lycopene has the ability to provide protection by inducing apoptosis, inhibiting metastasis, preventing oxidative stress, and upregulating the antioxidant response so that cells can produce cytoprotective enzymes [38]. Although these studies have shown the involvement of these biological processes in protecting against cancer, the exact mechanisms of this action, including cell cycle arrest and apoptosis, still remain unclear [40], and this contributes towards the need for more research into the use of lycopene and other natural products in general for the treatment and/or management of cancer.

A study undertaken by Jeong et al. assessed the anti-cancer effect of lycopene on pancreatic cancer PANC-1 (pancreatic carcinoma) cells by determining its impact on cell viability and apoptotic indices by measuring the levels of active caspase-3 [41]. Caspases are a family of endoproteases that provide critical links in cell regulatory networks, controlling inflammation and cell death [42]. Activation of these apoptotic caspases results in the generation of a cascade of signaling events that allow the controlled demolition of cellular components, also known as apoptosis. It is the dysregulation of these caspases which can promote the development of human diseases, such as cancer and inflammatory disorders.

Moreover, the Jeong et al. study provided evidence that lycopene induced apoptosis of pancreatic cancer PANC-1 cells and resulted in an increased level of active caspase-3, suggesting that its supplementation could decrease the risk of pancreatic cancer. This study was designed to assess the effects of lycopene on cancer cell survival; however, it also indicated that the cell viability was dose-dependent. Although this is suggestive that lycopene can have a protective effect against cancer, more in-depth research is required to determine a safe dosage, as well as to find a way to implement this information to create treatment options safe to use for all types of cancer cells.

Another study conducted by Tjahjodjati et al. offered similar results to the study conducted by Jeong et al. and assessed the effect of lycopene on human prostate cancer cells by measuring caspase-9 concentration as a marker of apoptosis in cells [43]. The study also showed an increase in caspase-9 levels, suggesting an increase in apoptosis, but was dependent on the dosage of lycopene used. Although this study approved the concept of lycopene inducing apoptosis, another study conducted by Salman et al., in which four different cell lines, including human colon carcinoma (HuCC), B chronic lymphocytic leukemia (EHEB), human erythroleukemia (K562), and Raji, a prototype of the Burkitt lymphoma cell line [44], were treated with lycopene, it was shown that lycopene was able to induce apoptosis in the Raji cells only and was ineffective in inducing apoptosis in the other three cell lines. Lycopene is readily available in a number of food-based products, and this may prove useful in the treatment of cancer.

2.5. Ursolic Acid and Cancer

Ursolic acid (UA) is a natural compound found in the leaves of various plants, including rosemary, marjoram, lavender, oregano, thyme, and lemon balm, as well as being found in apple skin, berries, and flowers. It is reported to possess various beneficial pharmacological properties. These include anti-inflammatory, anti-oxidant, anti-microbial, anti-diabetic, anti-obesity, and anti-carcinogenic effects [45–47]. Multiple studies have been conducted on various cancer types to investigate how UA affects cellular mechanisms and to show UA's efficacy against cancer cells by the analyses of various different pathways associated with tumorigenesis and cell proliferation, with results showing promise in the cancer cell response to UA treatment. Shan et al. [48] demonstrated that UA significantly inhibited proliferation and induced apoptosis in HT-29 cells by EGFR/MAPK inhibition. Kim et al. [49–51] also showed that UA induced apoptosis in HCT116 and HT29 (both colorectal cancer) cells via the inhibition of JAK2/STAT3 and the upregulation of miR-4500. Another study conducted by Zhang et al. [52,53] identified the suppressive potential of UA on invasive CRC cells, singling out UA's role in the regulation of the TGF-β1 signaling pathway.

Evidently, UA has been shown to possess potentially significant anti-cancer properties, affecting multiple pathways relating to tumorigenesis, cell proliferation, and cell apoptosis [49–60]. This, therefore, makes UA a prime candidate for a potential alternative chemotherapeutic agent. However, precisely how UA exacts these mechanisms is yet to be fully elucidated [49–51,54]. To further assess UA's effectiveness and to evaluate the mechanistic influence UA has on cancer-related pathways, further investigations analyzing the pathway mechanism and response to UA are required.

Moreover, multiple studies have shown the use of similar UA doses to treat various types of CRC and other cancer cell types in vitro and in vivo and have demonstrated a successful inhibition of cell proliferation, apoptosis induction, and migratory suppression [49–51,56–58], with the highest UA dose for Western blot analysis at 60 μM. In addition, Wang et al. [58] initially utilized a range of 0 μM to 400 μM for cell viability assays, but for subsequent cellular assays, they utilized a range of 0 μM to 60 μM, due to the significant suppressive ability shown at doses less than 60 μM.

Evidently, the experimental dose of UA used is in line with other conducted studies in which UA treatment is deemed successful. Although increasing the dose beyond 50 μM does suggest providing significant results [49–51,58], experimental doses of 20 μM and 50 μM should provide some significant results, as seen with the studies mentioned above. This implies that factors other than UA dose are affecting this experiment. One striking difference between this experiment and the studies mentioned is the incubation time of the UA-treated cells. The experimental incubation time of 4 h is comparatively lower than those of the studies mentioned. Wang et al. [53] incubated UA-treated cells for 48 h for all assays and analyses that were conducted. Kim et al. [49] used various times but fixed incubation times for different assays, using 72 h for Western blot analysis and 48 h for other tests. Meanwhile, Wang et al. [58] employed a range of incubation times for different assays for the cell viability assay (24 and 48 h) and scratch wound assay (0, 6, and 12 h), in which they concluded that the inhibition of the growth of cell lines and their ability to invade and migrate were proportional to the dose and time of treatment.

Overall, studies conducted on investigating UA effects on cancer have shown successful results, in which all conclude that UA effectiveness is dependent on the dose or dose and time of UA treatment [49–60]. Hence, a way to further improve experimental results would need to employ greater incubation times and a wider dose range to further validate dose and time proportionality.

The summary of the natural products discussed here and their mechanisms of action on cancer can be found in Table 1.

Table 1. Natural products and their mechanisms of action on cancer.

Natural Products Extraction	Bioactive Compound(s)	Common Method of Extraction	Cancer Use	Mechanism of Action	Targeted Key Signaling Pathways	Side Effects	Other Therapeutical Roles
Ajwa date (*Phoenix dactylifera* L.)	-Phytosterols, Polyphenols, Flavonoids and Glycosides	-Ethanol based extractions -Methanol based extraction	-Breast cancer, Colorectal cancer, hepatocellular carcinoma, and Prostate cancer	-Restricts cancer progression and development -Cell shrinkage -Cell apoptosis and cell cycle arrest	-Stimulation of p53 mediated cell signalling -Downregulation of Bcl-2 pathway -Downregulation of AKT/mTOR pathway	-No reported side effects	-Anti-diabetic activity in controlling blood glucose -Ant-inflammatory activity -Anti-microbial andante-bacterial activity -Neuroprotective effect
Curcumin	-Polyphenol	-Fractionated by silica gel 60 column chromatography	-Breast cancer, Colon cancer, Pancreatic cancer, Bladder and Prostate cancer	-Inhibits proliferation, survival, metastasis, invasion, and angiogenesis -Modulates cell growth and cell cycle -Stimulates apoptosis -Induces cell cycle arrest	-Stimulation of Caspase death receptor pathway -Induces WNT/-catenin β pathway -Downregulation of NFkB signalling -Inactivation of the PI3K/Akt pathway	-May promote Liver impairment in individuals with jaundice	-Anti-diabetic effect -Anti-inflammatory activity -Antioxidant activity -Anri-bacteria, anti-fungal, anti-microbial activity -Analgesic
Ginseng	- Ginsenosides, Alkaloids and Gintonin	- Liquid-solid column chromatography.	-Melanoma, Cervical carcinoma, and Lung cancer	-Induce apoptosis -Reduces cell viability	-Induces WNT/-catenin β pathway -Inhibition of CREB/MITF pathway	-Anti-coagulant ginseng interaction -Allergic reaction -Cardiovascular toxicity	-Hypotensive -Anti-oxidant activity -Sedative -Analgesic role

Table 1. *Cont.*

Natural Products Extraction	Bioactive Compound(s)	Common Method of Extraction	Cancer Use	Mechanism of Action	Targeted Key Signaling Pathways	Side Effects	Other Therapeutical Roles
Lycopene	-Lycopersicum esculentum	-Hexane- based extractions -Acetone-based extractions -Ethanol-based extractions	-Prostate cancer, Colon carcinoma, B-chronic lymphocytic leukaemia, erythroleukemia, and Burkitt lymphoma	-Induces apoptosis -Inhibits metastasis -Prevents oxidative stress	-Stimulation of Caspase-3 and -9 death receptor pathway	-Orange-coloured appearance 'lycopenemia' -Diarrhoea -Allergic reaction	-Mitigates metabolic diseases -Anti-diabetic -Anti inflammatory -Neuroprotection -Sperm quality enhancement and fertility promotion
Ursolic acid	-Pentacyclic Triterpenoid	-Ethyl-acetate extractions	-Colon adenocarcinoma	-Inhibits proliferation and tumorigenesis -Induces apoptosis -Inhibits migration and invasion	-Inhibition of JAK2/STAT3 pathway -Inhibition of EGFR/MAPK pathway -Regulation of TGF-β1 signalling pathway	-Nausea -Gastrointestinal (GI) problems	-Anti-inflammatory -Anti-oxidant -Anti-microbial -Anti-diabetic -Anti-obesity

2.6. Approved Anticancer Drugs from Medicinal Plants

Novel natural medicinal products are regularly published, and several are reported to have therapeutic potential for combating cancer. Anticancer drug discovery from natural therapies has led to the identification of novel compounds that have been approved as therapeutic agents [61,62].

2.6.1. Anticancer Natural Products

Approved therapeutic natural products in the market fall into five categories. Firstly, there are the monoterpene indole vinca alkaloids isolated from Malagasy periwinkle, *Catharanthus roseus* (L.) G. Don., vinblastine and vincristine, which are used to treat several adult and pediatric malignancies, including germ cell tumors, both Hodgkin and non-Hodkin's lymphoma, neuroblastoma, and lung cancer [61,62]. These alkaloids act as antimicrotubule agents that act by blocking mitosis through the arrest of cells in the metaphase, being cell cycle phase-specific for the M and S phases. The alkaloids prevent the polymerization of tubulin to form microtubules and also by inducing the depolymerization of mature tubules, leading to the disorder of microtubule assembly during mitosis and subsequent metaphase arrest in the cell [61,62].

The second category includes the taxane derivative paclitaxel, which is isolated from Pacific yew, *Taxus brevifolia* Nutt, and traded as taxol or abraxane. Taxol is used to treat Kaposi's sarcoma and cancers of the lung, ovaries, and breast. Generally, Taxol is an antimicrotubule agent, which interferes with the normal growth of microtubules. It is proposed that Taxol works by inhibiting both cell proliferation and cell death, and at lower concentrations, it hyperstabilizes the spindle during mitosis, thereby blocking mitosis, leading to the inhibition of cell proliferation and the induction of apoptosis [63]. This works by destroying the cell's ability to use its cytoskeleton in a flexible manner, and specifically, Taxol binds to the β-subunit of tubulin. In higher concentrations, Taxol adopts the mode of action of the vinca alkaloids by increasing the polymerization of microtubules and stimulating the formation of microtubule bundles, thereby blocking entry into the S phase. This tends to result in the inhibition of cell proliferation [63].

The third category includes the lignan derivative podophyllotoxin isolated from mayapple, *Podophyllum peltatum*, and its semisynthetic etoposide and teniposide that are used to treat testicular cancer, lung cancer, lymphoma, leukemia, neuroblastoma, and ovarian cancer [64,65]. The natural compound podophyllotoxin is traded as condylox and podofilox and it is used to treat external genital warts and perianal warts. The mode of action of this compound is not well understood but is proposed to bind and inhibit topoisomerase II during the late S and early G2 stages, interrupting the temporary break caused by the enzyme, thereby disrupting the reparation of the breakthrough which the double-stranded DNA passes, consequently stopping DNA unwinding and replication [65].

Podophyllotoxin is synthesized to etoposide, which is used to treat testicular and cell lung tumors. Etoposide is sold as etopophos, toposar, and vepesid and works by inhibiting DNA topoisomerase II, thereby preventing DNA re-ligation, resulting in crucial errors in DNA synthesis at the premitotic stage of cell division. In turn, this leads to apoptosis of the cancer cell. Etoposide is proposed to be cell cycle-dependent and phase-specific by affecting the S and G2 phases of cell division. Therefore, etoposide inhibits the topoisomerase II alpha isoform and the β-isoform, resulting in its carcinogenic effect [65].

Podophyllotoxin is also derivatized to teniposide, which is used as an adjunct for chemotherapy induction for treating refractory childhood acute lymphoblastic leukemia. Teniposide works by inhibiting type II topoisomerase activity, as it does not intercalate into DNA or bind strongly to DNA. This drug binds to and inhibits DNA topoisomerase II [65–67].

The fourth category includes the camptothecin derivatives irinotecan and topotecan, isolated from the happy tree, *Camptothca acuminata*. Camptothecin was investigated for the treatment of cancer, showing strong activity in preliminary clinical trials, as well as low solubility and adverse drug reaction. Several semisynthetic derivatives, including irinotecan, traded as Camptosar and Onivyde, and topotecan are used to treat metastatic carcinoma of the colon or rectum and pancreatic cancer. They prevent the relegation of the DNA strand and prevent it from joining together with the topoisomerase I-DNA complex. The formation of this ternary complex affects the mobile replication fork, subsequently inducing replication arrest and double-stranded breaks in DNA. This means DNA damage is not efficiently repaired, and apoptosis results [66,67].

The fifth category includes the combretastatins, which include several *cis*-stilbenes from the South African shrub Cape bushwillow, *Combretum caffrum* (*Combretaceae*). The compounds of the combretastatin class, including the two naturally occurring combretastatin A1 and combretastatin A4, indirectly act on cancer cells by inhibiting the polymerization of tubulin. This results in the disruption of the tumor endothelial cells lining the tumor vasculature and vascular collapse in solid tumors [68]. A phosphate prodrug of combretastatin A4, combretastatin A4 phosphate, is approved by the FDA for the treatment of a range of thyroid and ovarian cancers [69].

Various alternative plant-derived anti-cancer compounds include ingenol mebutate, homoharringtonine, and the combretastatins. Ingenol mebutate is isolated from the native Australian plant *Euphorbia peplus* (*Euphorbiaceae*). It is an approved drug used as a treatment for actinic keratosis, a skin condition resulting from too much exposure to ultraviolet radiation. This, in turn, may lead to squamous cell carcinoma, if not treated. Ingenol mebutate tends to have two main mechanisms of action. Firstly, it induces the rapid induction of cell death in the treated area at high concentrations of over 200 μM, and at lower concentrations of about 0.1 μM, it activates an inflammatory response capable of eliminating the residual cells [70]. Homoharringtonine is a cephalotaxine alkaloid that is present in the *Cephalotaxus* genus (*Cephalotaxaceae*) and is being used in the treatment of chronic myeloid leukemia (CML) [71]. A derivative of homoharringtone, omacetaxine mepesuccinate, is effective in the treatment of various myelodysplastic syndromes and chronic myelomonocytic leukemia [72].

There are several potential anticancer agents, including the benzylisoquinoline alkaloids from the opium poppy, *Papaver somniferum,* which includes noscapine, that are known to exhibit anticancer potential. Noscapine has been investigated for use in the treatment of lymphoma (non-Hodgkin's), leukemia (lymphoid), and multiple myeloma [73].

Recently, annonacin isolated from *Annona muricata* L., which was identified as a popular medicinal plant in treatment regimens among cancer patients in Jamaica, has been demonstrated to have anticancer effects against DU-145 prostate carcinoma cells, with IC_{50} values of 0.1 ± 0.07 μM [74].

Drimianins C and D from African *Drimia altissima* have showed anticancer activities at the nanomolar level against a number of human cancer cell lines in the NCI-60 screen [75].

An extract rich in artocarpin derived from *Artocarpus heterophyllus* Lam was demonstrated to have both concentration-dependent and time-dependent cytotoxicities against human colorectal HCT116 cells, with an IC_{50} value of 4.23 mg/L in 72 h [76]. In the study, Morrison et al. demonstrated that the artocarpin-rich extract contained chemopreventive, cytotoxic, anticancer, and anti-inflammatory responses and minimal toxicity, validating that the *A. heterophyllus* extract can be a potential therapeutic agent.

2.6.2. Potential Side Effects of Natural Products

According to current research, Ajwa dates have shown no harmful side effects in either healthy individuals or cancer patients. Ajwa has been recognized for its preventive and therapeutic benefits, primarily due to its phytochemical and nutritional properties [77].

In contrast, while curcumin is known for its anti-inflammatory and anti-carcinogenic properties, it has been associated with potential liver damage in cases of suspected drug-induced liver injury. A recent prospective study, updated in March 2022, reported that curcumin extracts from turmeric were linked to instances of jaundice and elevated bilirubin levels in some patients [78]. It is crucial to note that turmeric-related hepatotoxicity was observed in individuals taking commercially available turmeric supplements containing piperine (black pepper), which is known to enhance curcumin's systemic bioavailability. Therefore, further research is needed to confirm the potential of curcumin to induce liver injury [78].

Recently, there have been growing concerns about the use of ginseng in patients taking anticoagulants like warfarin for stroke prevention or thromboembolism. Recent case reports indicate that patients using ginseng for energy have experienced emergency hospital visits due to interactions between ginseng and warfarin. A study by Dong et al. [79] found that ginseng may antagonize the anticoagulant effects of warfarin, leading to decreased warfarin concentrations in the blood. This research provides evidence highlighting ginseng intervention with warfarin and its anticoagulant activity.

Moreover, while ginseng has shown potential as a cytotoxic agent and seems to cause less mast cell degranulation, there are concerns that ginseng extracts might significantly increase histamine release, which could make ginseng a potential allergen capable of triggering anaphylactic reactions [80]. Although ginseng is generally considered safe and non-toxic, some evidence suggests that excessive use may lead to irreversible damage to vascular contractility by blocking calcium ions in vascular smooth muscle cells [81]. This could contribute to cardiotoxicity and increase the risk of ischemic attacks, potentially resulting in hypertensive crises in patients [82]. However, further studies are needed to clarify the clinical interactions related to ginseng misuse and its connections to anticoagulant interactions, allergies, and cardiovascular toxicity.

Lycopene is a compound of botanical origin that may exert unfavorable side effects if consumed or applied in excess. As a carotenoid pigment, its consumption may lead to the deposition of it in skin, which may lead to an orange-colored appearance dubbed 'lycopenemia', as well as slight mutagenic activity of the products upon degradation due to poor storage [83], which may initiate cancer cells if ingested consistently. Lycopene has relatively very mild side effects compared to those of chemotherapy, as even after a 13-week study based on rats and lycopene administration, there was been no significant effect on their physiology and biochemistry [84].

Ursolic acid has the ability to lower both diastolic and systolic blood pressure, due to the molecule's cardioprotective properties via vasodilation [85] in vivo. This vasorelaxant property may be useful for hypertensive patients but may be counterproductive in those with low blood pressure. Considering the low bioavailability of ursolic acid due to subpar water insolubility, intravenous and intragastric injections are used for administration for increased effectiveness, causing nausea and gastrointestinal problems to occur independently of the therapeutic's biochemical effect.

3. Conclusions

Natural therapies provide a cost-effective and easily accessible source of potential treatment or management of both chronic and severe diseases, including cancer. The lack

of widespread healthcare in many developing countries makes the discovery of natural compounds to help combat this disease even more relevant.

The Ajwa date has been shown to contain a range of phytochemicals, such as phytosterols, polyphenols, flavonoids, and glycosides, which have anti-inflammatory, antioxidant, cardioprotective, hypolipidemic, and anticancer properties. Various cancer cells have shown shrinkage and loss of cytoskeletal structure, including chromatin condensation and DNA fragmentation through apoptosis in the presence of the extracts of these compounds. Curcumin, which is a yellow coloring present in spices such as turmeric, has also gained increased interest in cancer prevention and treatment due to being non-toxic, multi-cite-targeted, and cost-effective. It can inhibit the major stages of cancer progression, including proliferation, survival, invasion, metastasis, angiogenesis, and chemoresistance in various tumor cell lines. This role is primarily attributed to its interference with multiple cellular signaling cascades, including Wnt/β-catenin, PI3K/Akt/mTOR, JAK/STAT, MAPK, NFkB, VEGF, and p53, as well as various genes, like cyclin D1, TP53, BAX, BCL-2, and MMPs, which are known to modulate cellular growth, the cell cycle, and the apoptosis of tumors. Ginseng has been used for centuries in the treatment of a wide range of diseases. The three types of ginsenosides present are triterpenoid saponins, which have been shown to induce apoptosis in HeLa and MS751 cells and reduce A549 and H1299 tumor cell proliferation. This may be through the lowered expression of the CREB (cAMP response element binding protein), MITF, and tyrosinases in B16BL6 melanoma cells and the inhibition of the CREB/MITF pathway. In addition, the ginseng alkaloid harman is cytotoxic to PC12 cells. Ginseng itself seems to work through the WNT pathway in 528NS cells. Lycopene is an acyclic A-carotene responsible for the characteristic red pigmentation of ripe tomatoes and other fruits, such as watermelon and papaya. They can induce apoptosis, slowing down metastasis, preventing oxidative stress, and enhancing the antioxidant response, allowing cells to produce cytoprotective enzymes. Studies on human pancreatic and prostate cancer cells showed that apoptosis was accompanied by increased levels of active caspase-3 and caspase-9. Other studies have shown that lycopene was active in Raji cells only. Ursolic acid is found in the leaves of many herbs. It has been shown to significantly inhibit proliferation and induce apoptosis in HT-29 cells by EGFR/MAPK inhibition and in HCT116 and HT29 cells via the inhibition of JAK2/STAT3 and the upregulation of miR-4500 and of the TGF-β1 signaling pathway.

Thus, there has been a wide use of natural products as phytochemicals in cancer prevention and treatment. Several of these studies have shown some success, and their mechanisms of action have often been elucidated. As discussed earlier, since cancer chemoprevention and treatment using pharmacognosy approaches present such a useful approach, further research to thoroughly understand their efficacy, PK parameters, metabolomics, toxicities, and drug–herb interactions is urgently needed. This would be followed by the development of formulations, stabilities, and dosage treatment schemes. Although industrial participation in natural product research has been scaled back in recent years, the search for new drugs will continue to be a promising and active research domain for years to come.

Author Contributions: Conceptualization, A.E., N.W., H.M., J.B. and M.K.L.; writing—original draft preparation, A.E., N.W., H.M., J.B., M.K.L., S.K., A.S., N.H. and S.M.G.; writing—review and editing, A.E., N.W., H.M., J.B., M.K.L., S.K., A.S., N.H., S.M.G., E.C., N.D. and V.J.R.; supervision, A.E., N.W. and H.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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