



Functional foods' bioactive components and their chemoprevention mechanism in cervical, breast, and liver cancers: A systematic review

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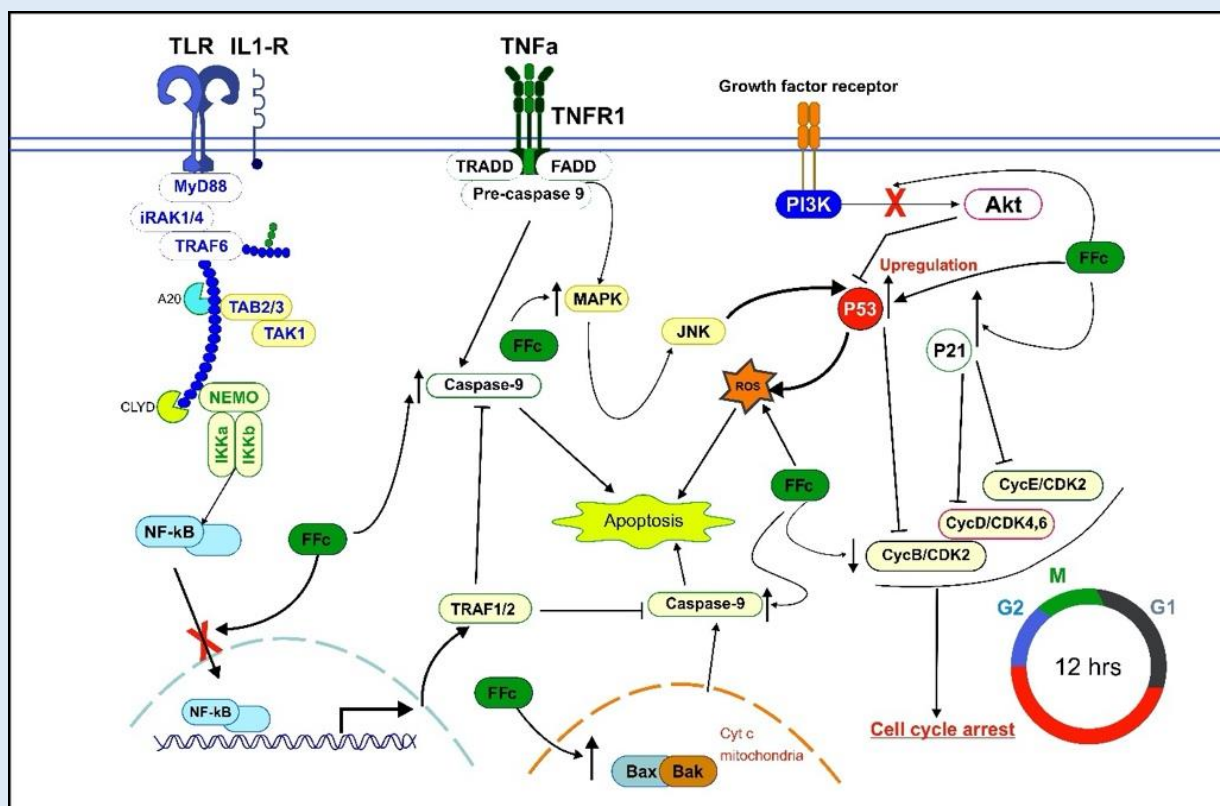
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ABSTRACT

The invasiveness and low survivability on the part of patients associated with cancer continues to raise global concern. Different approaches have been used in the treatment and restoration of normalcy in cancer patients. However, most of the therapeutic strategies employed are challenged with high cost, low efficacy, high toxicity, and multiple side effects. In recent times, emergent studies have provided evidence that functional foods and their bioactive components serve roles as potential agents in the prevention and treatment of cancers. Moreover, global interest has focused on how this chemoprevention potential of functional foods can be explored as plant-based medicines for drug development. Although, the literature is replete with the mechanism of chemoprevention elicited by individual components of functional foods, there are limited reports on their overall anti-cancer mechanisms.

Therefore, this systematic review aims to unify the anti-cancer mechanisms of functional foods in cervical, breast, and liver cancers which were selected due to their high incidence and mortality globally. We reviewed articles from NCBI/PUBMED from 2010 until February 2020. Three different search words used include “Functional food and cervical cancer”; “Functional foods and breast cancer”; “Functional foods and hepatocarcinoma”. Consequently, 434 scientific papers resulted from the three search words. However, after applying the inclusion/exclusion criteria, 37 articles were selected: 14 on cervical cancer, 10 on breast cancer, and 13 on hepatocellular carcinoma. We subsequently emphasize the anti-cancer mechanisms of various functional foods in the studies selected and these include induction of apoptosis, cell cycle arrest, disruption of microtubular network, downregulation of anti-apoptotic Bcl-2 family expression, induction of autophagy, modulation of signaling cascades, ROS generation, and suppression of specific genes. Therefore, functional foods possess effective chemoprevention mechanisms which can be explored in drug development.

Keywords: Cervical cancer, Breast cancer, Liver cancer, Cancer prevention, Functional foods, Bioactive compounds



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1.0 INTRODUCTION

The beneficial influence of bioactive food components has been the subject of many studies. [1-4]. Foods that contain bioactive ingredients are referred to as functional foods as they provide medical benefits other than their nutritional value [5]. They may provide the body with the

appropriate quantity of biomolecules needed for its healthy upkeep [6]. Functional foods and conventional food can appear similar. However, differences between functional foods and conventional foods have been established. The physiological significance of functional foods has been demonstrated to include a reduction in

risk and vulnerability to chronic diseases beyond the elementary nutritional significance and maintenance of gut health [6]. A document of the Functional Food Science in Europe (FUFOSE) elaborated the definition of Functional Foods to include those foods which “beneficially affect one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease” [7-8]. Such food with pro-health benefits [5] may be prophylactic [2,5,7,9-10].

In the mid-1980s, the term “Functional Foods” was first introduced in Japan and has been described as processed foods, which in addition to being nutritious consists of ingredients that enhance specific bodily functions. The Foods for Specified Health Use (FOSHU) is a specific regulatory approval process for functional foods in Japan, with such foods bearing a seal of approval from the Japanese Ministry of Health and Welfare [11]. Meyer reported that Functional Foods made by health-conscious baby boomers are the leading trend in the United State food industry [12], with a market value at \$28.9 billion [13]. More important is the potential of Functional Foods to mollify diseases, improve health, and minimize health care costs [13].

Functional foods can contain various proportions of nutrients (such as vitamins, minerals, fibers, electrolytes among others) alongside numerous naturally occurring bioactive substances in plant foods called phytochemicals. Such foods of plant origin possess antioxidant activity, which is one of the numerous anti-cancer properties. Other health-promoting properties of plants include anti-proliferative, anti-inflammatory, antipyretic, analgesic, anti-viral, anti-bacterial, and neuroprotective activities [14]. These plants include

fruits, vegetables, beans, legumes, nuts, whole grains, herbs, and spices [15]. Phytochemicals (some are also known as phytonutrients) are naturally occurring substances produced in certain metabolic pathway in plants. Some have been shown to be responsible for the putative health benefits of plant-based foods. Phytochemicals have been classified based on their structure and properties such as flavonoids, flavonols, flavanols, proanthocyanidins, and procyanidins [16] and also include carotenoid, other phenolic compounds, phytosterols and phytostanols, tocotrienols, organosulfur compounds, non-digestible carbohydrates, saponins, salicylates, glucosinolates, protease inhibitors, monoterpenes, phytoestrogens, terpenes, lectins and many more [17].

Cancer is a multifactorial disease, which remains a global concern and has been adjudged to be idiopathic in several cases though could be triggered by several factors which include radiation, chemical, and viruses among others [18]. Cancer has a long history, recorded as far back as 3000 BC, and has so much sporadically increased to have claimed millions of lives worldwide. In 2020, approximately 19.3 million new cases and 10 million mortalities were announced. 1 of every 5 men and 1 of every 6 women globally developed cancer in their lifetime, and 1 out of 8 men and 1 out of 11 women died as a result of cancer. Globally, the total sum of people who are alive during 5 years of their cancer diagnosis, named the 5-year prevalence, is approximately 20.6 million. The burden of cancer increases as a result of population growth, aging, and direct link between some types of cancer and socio-economic development [19]. The International Agency for Research on Cancer (IARC) has estimated the cancer incidence rate based on gender to be one-in-five men and one-in-six women globally.

These subjects have the tendency to develop cancer over the course of their lifetime, and the mortality rate is one in eight men and one in eleven women [20]. Several factors appear to be the driving force for this observed increase, most especially a growing and aging global population and an exponential increase in exposure to cancer risk factors and carcinogenic substances [20]. The continent of Asia accounts for nearly half of the reported new cancer cases globally and more than half of cancer-related deaths. Asia and Africa have a higher proportion of death due to cancer (7.3% and 57.3% respectively) compared with their incidence rate (5.8% and 48.4% respectively). IARC suggests this trend is likely due to the higher frequency of cancer types associated with poorer prognosis, along with limited access to timely diagnosis and treatment [18].

Cervical cancer, otherwise called cancer of the cervix, is associated with the lower and narrower end of the uterus. The cervical canal connects the uterus and the vagina of the female reproductive system. However, cervical cancer and breast cancer ranks as the most common female malignancies when both incidence and mortality rates are being considered on a global scale. More than 200,000 cancer-related deaths are reported due to cervical cancer each year, predominantly among economically disadvantaged women in both developing and industrialized nations. The world's highest rates of cervical cancer incidence and death are from sub-Saharan Africa, including South Africa with a rate of 40/100,000. Cervical cancer is a public health challenge as it is the commonest female genital tract cancer worldwide.

Breast cancer is the most frequently occurring cancer and the leading cause of death in women between the ages of 20 and 59 years in the United States [21]. It is

estimated that about one in eight US women will develop invasive breast cancer over the course of her lifetime. In 2018, over 266,000 new cases of invasive breast cancer were expected to be diagnosed in women in the U.S., along with nearly 64,000 new cases of noninvasive breast cancer in US women [22-23]. As of January 2018, there are already more than 3.1 million US women with a history of breast cancer, which includes the women currently being treated as well as women who have undergone a treatment plan. Furthermore, it is the second most common cancer in terms of both incidence and mortality in African women. Notably, breast cancer has a complex etiology where susceptibility is influenced by both environmental and genetic factors. Considerable experimental and epidemiological evidence suggests that lifetime exposure to endogenous hormones, such as estrogens and androgens, promotes breast carcinogenesis. The extensive molecular and pathological diversities observed in breast cancer patients suggests that breast cancer is not a homogeneous disease that can be effectively managed by a "standard of care" approach [24]. Liver cancer is often fatal and occurs worldwide. The liver is an essential organ that plays major and vital roles in the metabolic economy of the body. As a result of its central role in survival and existence, it is exposed to a barrage of antigens and xenobiotics, some of which are infectious and sometimes carcinogenic. Liver cancer is majorly divided into two categories, those being, primary liver cancer and secondary or metastatic liver cancer. In countries with low prevalence of Hepatitis B virus (HBV) infection, liver metastases are the major cause of liver cancer death induced by secondary liver cancer, while in regions with high prevalence of HBV such as China and sub-Sahara Africa, Hepatocellular carcinoma (HCC) accounts for most of the liver cancer cases. It is however common in regions of the world where risk factors are more prevalent. Worldwide, HCC is the sixth most

common cancer, the fifth most common cancer in men, and the eighth-most common in women. Most of the over 600,000 annual deaths attributable to HCC occur in Asia and sub-Sahara Africa, mainly because of the endemicity of the major risk factors [25].

The emerging role of functional foods in the prevention, treatment, and management of various cancers viz a viz cervical, breast, and liver cancer is increasing and within which lies an area of global interest in research for novel functional foods. Therefore, elucidation of their molecular mechanisms and interactions may fulfill an overall goal of how they exert their anticancer, anti-proliferative and anti-tumor effects in various cancers.

2.0 METHODS

The authors reviewed articles from NCBI/PUBMED until February 2020 while taking into account certain inclusion and exclusion factors. Since three different types of cancer were considered, thus, three different search words were used to collect data from the database: “Functional food and cervical cancer”, “Functional foods

and breast cancer”, and “Functional foods and hepatocarcinoma”. The inclusion factors considered by the authors are, (1) publications within the last 10 years on cervical cancer, and 5 years for breast and liver cancers, (2) original research articles, (3) both *in vivo* and *in vitro* studies were considered, and (4) works related to the author’s consideration. However, review articles, unrelated works, and synthetic functional food were excluded.

3.0 RESULTS

There were 434 scientific papers resulting from the search on PubMed – 43 search results are related to cervical cancers, 289 are related to breast cancer, and 102 are related to hepatocellular carcinoma. However, after applying the inclusion and exclusion factors, 37 articles were selected in total – 14 articles on cervical cancer, 10 articles on breast cancer, and 13 articles on hepatocellular carcinoma. Figure 1 and tables 1, 2, and 3 below summarize the articles selected.

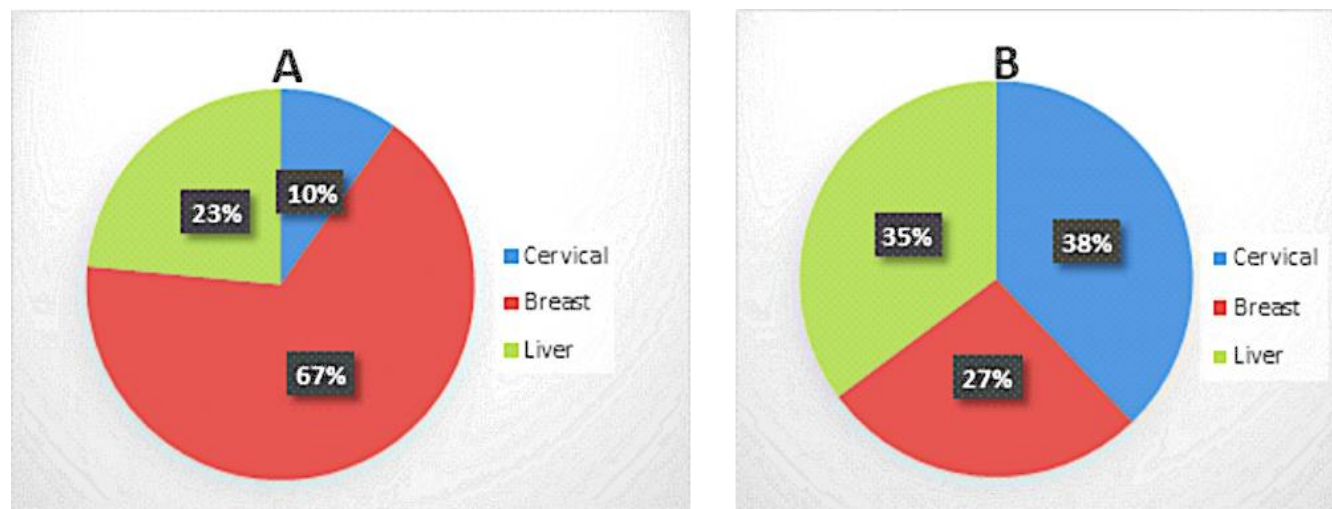


Figure 1. The distribution in percentage of articles obtained from pool of search and the percentage of articles finally selected for the review.

Table 1. Summary of articles in this review: cervical cancer

Author	Title	Functional Food Component	Methods	Results	Conclusion
[25]	Arabinogalactan derived from <i>Lycium barbarum</i> fruit inhibits cancer cell growth via cell cycle arrest and apoptosis	Arabinogalactan (LBGP-I-3)	Purification of <i>L. barbarum</i> fruit by alcohol fractional precipitation and evaluation of its effect on cancer cells	Impaired growth of MCF-7 cells, SMMC-7721 and HeLa-cervical cancer cell (cell viability of 55.94%)	LBGP-I-3 may be a potential anticancer functional food for the prevention (prophylaxis) of cancer.
[26]	Methyl protodioscin from <i>Polygonatum sibiricum</i> inhibits cervical cancer through cell cycle arrest and apoptosis induction	Methyl protodioscin	Methyl protodioscin was purified from <i>P. sibiricum</i> and applied to the cervical HeLa cell lines, for analysis ex post facto.	Inhibition of HeLa cell proliferation in a dose-dependent manner via changes in HeLa cell morphology, cell cycle repression, apoptosis and ROS generation	MPD can be incorporated as natural anti-cancer drug in therapeutic strategies.
[27]	Apoptotic effect of a phytosterol-ingredient and its main phytosterol (β -sitosterol) in human cancer cell lines	Phytosterol (PS)-ingredient (β -sitosterol)	Human breast (MCF-7), colon (HCT116) and cervical cancer (HeLa) cells were cultured, seeded and treated with tall oil PS-ingredient or β -sitosterol at different concentration with subsequent viability assay, cell cycle analysis and assessment of apoptosis	Overall reduction in cell viability. Absence of dose-response effect of PS on MCF-7 and HCT116 cells. However, there was a dose-response effect on HeLa cell.	As much as further research is encouraged, current data surmised that, PS-ingredient may be referred to as anticarcinogenic substance against colon, breast and cervical cancers.
[28]	Biotin-Modified Poly(lactic-co-Glycolic Acid) Nanoparticles with Improved Antiproliferative Activity of 15,16-Dihydrotanshinone I in Human Cervical Cancer Cells	15,16-Dihydrotanshinone I (DI)	Encapsulation of DI into DI-PPA-NPs and DI-BPA-NPs copolymers and the evaluation of its antiproliferative activity on the human cervical HeLa cells.	Free DI and the copolymers impaired growth of HeLa cells in dose and time dependent fashion.	There is enhancement of the growth impairment ability of DI when incorporated into copolymer thereby further showing its potential use as cancer therapy.
[29]	LC-ESI-TOF-MS and GC-MS profiling of <i>Artemisia herba-alba</i> and evaluation of its bioactive properties	di-O-caffeoylquinic acids, artemisinic acid, menthol, α -ketoglutaric acid, scopolin, isoschaftoside and sucrose.	Component identification using LC-ESI-TOF-MS and GC-EI-MS. Cell – MCF-7 breast cancer and HeLa human cervical cell lines - viability assay.	Dose-dependent inhibition of cellular proliferation of HeLa (15 μ g/ml) and MCF-7 (70 μ g/ml) cell	<i>Herba alba</i> can be alternatively used as bioactive component in functional foods, nutraceuticals and dietary supplement.
[30]	Molecular mechanism of anti-cancerous potential of Morin extracted from mulberry in HeLa cells	Morin	Morin extraction and purification with HPLC followed by treatment on HeLa cell. Cell viability (MTT assay), Flow cytometry for cell cycle and apoptosis analysis etc.	Inhibition of HeLa cell proliferation, morphological changes, cancer cell cycle arrest and induction of apoptosis in dose-dependent fashion	New treatment strategy in the future will involve the synergy of morin and other anti-cancer molecule, and as functional food, it can elicit its anti-neoplastic effects.
[31]	Dietary flavonoids, luteolin and quercetin, inhibit invasion of cervical cancer by reduction of UBE2S through epithelial-mesenchymal transition signaling	Luteolin and quercetin	Culturing of human cervical epithelial cancer cell A431-III cells. Cell viability assay-seeded cells were incubated with luteolin and quercetin at varying concentration overnight.	Inhibition of tumour invasion via the inhibition of ubiquitin E2S ligase expression (this expression was paralleled to the metastatic and invasive capacity of cervical cancer cells	Dietary luteolin and quercetin possesses autonomous ability to disrupt malignancy via the alteration of UBE2S expression

Author	Title	Functional Food Component	Methods	Results	Conclusion
[32]	Hazelnut (Corylus avellana L.) Shells Extract: Phenolic Composition, Antioxidant Effect and Cytotoxic Activity on Human Cancer Cell Lines	Neolignans, cedrusin, balanophonin, gallic acid etc.	Methanol extraction of different phenolic composition. DPPH scavenging ability and MTT cell viability assay for A375 (melanoma) and HeLa (cervical) cells	Proapoptotic effect and induction of apoptosis in A375 and HeLa cells through the cleavage of PARP-1 and caspase-3 activation	Hazelnut shell's extract might be useful as functional food component, dietary supplement and or ingredient of nutraceuticals
[33]	Antioxidant and antiproliferative activities in immature and mature wheat kernels	Phenolics and flavonoids	Ethanol extraction of phenolic content and MTT assay to determine the antiproliferative effect in human colon cancer (HT-29) and human cervical (HeLa) cell	Higher concentration of total phenolic content in immature wheat contributed inhibition of about 50% cell proliferation in HT-29 and HeLa cells than in mature wheat.	Immature wheat extract inhibited cell proliferation more strongly than mature wheat.
[34]	A detailed comparative study between chemical and bioactive properties of Ganoderma lucidum from different origins	Reducing sugars, organic acids, phenolic compounds, unsaturated fatty acids, tocopherols and ergosterol	Extraction and sulforhodamine B assay (cytotoxicity testing) using HeLa cell and four other human tumor cell lines	Ganoderma lucidum from Serbia showed growth inhibition upon its treatment on the five human cancer cell lines	The methanolic extract gave a promising antiproliferative effect without hepatotoxicity
[35]	Growth-Inhibitory Effects of Pigmented Rice Bran Extracts and Three Red Bran Fractions against Human Cancer Cells: Relationships with Composition and Antioxidative Activities	Phenolics, anthocyanin, and proanthocyanidin	MTT assay and determination of IC ₅₀	Red bran inhibited proliferation in leukemia, cervical and stomach cell lines.	Red bran can be used as functional food for human consumption
[36]	Lycium barbarum polysaccharide inhibits the proliferation of HeLa cells by inducing apoptosis	Lycium barbarum polysaccharide (LBP)	Preparation of LBP; MTT assay for cell viability; cell cycle analysis via flow cytometry and measurement of nitrite/nitrate concentration in HeLa cell medium	Inhibition of HeLa cell proliferation through dose dependent S phase cell cycle arrest, induction of apoptosis and NO-induced cell death.	LBP may be a potential drug for the control of cancer
[37]	Aqueous extract of ginger shows antiproliferative activity through disruption of microtubule network of cancer cells	Flavones and flavonols	Preparation of aqueous extract (GAE), culturing of HeLa cell, MTT cell viability assay, DNA synthesis analysis, cell cycle analysis and apoptosis analysis	Loss of cell viability in HeLa cell, increased population of subG ₀ /G ₁ phase and induction of apoptosis	GAE components can be further screened and used for the development of anti-cancer agent
[38]	Induction of apoptosis in human cervical carcinoma HeLa cells by polymethoxylated flavone-rich Citrus grandis Osbeck (Dangyuja) leaf extract	Flavonoids	Methanolic extract of <i>C. grandis</i> Osbeck, culturing of HeLa cell and other human tumour cell lines, cell viability assay and analysis of morphological changes	Leaf extracts diminished cell viability in a dose dependent fashion. Fraction also induce changes in cell morphology including; chromatin fragmentation and cell death	Dangyuja leaves contain functional component of poly methoxylated flavones which can prevent cervical cancer.

Table 2. Summary of articles in this review: Breast Cancer

Author	Title	Functional Food Component	Methods	Results	Conclusion
[39]	DT-13 inhibits breast cancer cell migration via non-muscle myosin II-A regulation in tumor microenvironment synchronized adaptations	Dwarf-lillytruf Tuber monomer-13 (DT-13)	Co-culturing system where tumor cells are co-cultured with hypoxia induced cancer-associated fibroblast or chemically induced cancer-associated adipocytes; cell migration analysis, western blot probe for expression analysis	Breast cell migration via stroma cells was directly influenced by Tumour Microenvironment (TME), however, TME dependent cell migration was inhibited by DT-13 by targeting NMII-A (Non-muscle myosin II-A)	TME is a prospective therapeutic target for the modulation of the loss of anchorage dependent growth in breast cancer.
[40]	The dietary c9,t11-conjugated linoleic acid enriched from butter reduces breast cancer progression in vivo.	c9,t11-conjugated linoleic acid	Urea complexation of FFA to obtain c8, t11-CLA, animal study, histopathological and immunochemistry	c9,t11-CLA decreased the tumor weight and volume, and reduced the tumor incidence up to 50% in the tumor induced rats.	The study confirms the preventive activity of c9,t11-CLA against breast cancer in animal models.
[25]	Arabinogalactan derived from Lycium barbarum fruit inhibits cancer cell growth via cell cycle arrest and apoptosis	Arabinogalactan (LBGP-I-3)	<i>L barbarum</i> fruit crude polysaccharide extraction and purification. Cell viability and colony formation assay.	The LBGP-I-3 showed strong inhibitory effect on MCF-7 cell proliferation by downregulating BCL-2/Bax expression and upregulating caspase-3, 8 and 9 among others.	LBGP-I-3 may be a potential anticancer functional food for the prevention (prophylaxis) of cancer.
[41]	Genistein Inhibits Proliferation of <i>BRCA1</i> Mutated Breast Cancer Cells: The GPR30-Akt Axis as a Potential Target.	Genistein	Expression of <i>BRCA1</i> , GPR30 and Nrf2. Effects of genistein on breast cancer cell viability and proliferation were assessed by the MTT, migration and clonogenic assays.	<i>BRCA1</i> silenced breast cancer cells treated with genistein resulted in the down-regulation of GPR30 expression causing reduction in cell viability, migration and colony formation.	Genistein is a chemopreventive isoflavone capable of suppressing cancer cell growth in <i>BRCA1</i> impaired breast cancer cells.
[42]	Vicilin - A major storage protein of mungbean exhibit antioxidative potential, anti-proliferative effect and ACE inhibitory activity.	Mungbean Vicilin Protein (MBVP)	Extraction and purification and antioxidant assay of mungbean protein. MTT cell viability assay against breast cancer cell lines MCF-7 and MDA-MB-231.	MBVP showed significant anti-proliferative activity and strong antioxidant capacity.	MBVP may serve as a physiologically active functional food in the treatment of breast cancer.

Author	Title	Functional Food Component	Methods	Results	Conclusion
[43]	The impact of Soy Isoflavones on MCF-7 and MDA-MB-231 breast cancer cells using global metabolomics approach	Soy Isoflavones	Treatment of soy extract with breast cancer cells and MTT assay. Proton NMR and GS-MS analysis.	Isoflavone elicited dose-dependent proliferative and cell death initiation activity. Modulation of glucose uptake suggested by metabolomics.	Metabolomics can be of immense help in understanding chemopreventive mechanisms of soy isoflavones, a potent functional food in breast cancer prevention
[44]	Antineoplastic effects of clove buds (<i>Syzygium aromaticum</i> L.) in the model of breast carcinoma	Phenolic acid, flavonol glucoside, tannins and phenolic volatile oils	MTS colorimetric assay was used to determine cytotoxic effects of extracts on MCF-7 cell lines. GC-MS and LC-MS analysis of extract.	In vitro studies showed pro-apoptotic and antiproliferative effects of extract in MCF-7 cells.	Regular consumption of Clove buds may be beneficial for the risk reduction of breast cancer.
[45]	<i>Pitaya pitaya</i> (<i>Hylocereus polyrhizus</i>) extract induces growth inhibition and pro-apoptotic effect on human cell lines of breast cancer via downregulation of estrogen receptor gene expression.	Anthocyanin	Extraction and quantification of antioxidant activities, determination of cell viability against MCF-7 and MDA-MB-435	Extract showed antitumor effect on breast cancer cell line by inducing apoptosis and suppressing BRCA1, BRCA2, PRAB gene expression	<i>Pitaya</i> may have strong therapeutic potential in the treatment and prevention of breast cancer.
[46]	Herbal remedies and functional foods used by cancer patients attending specialty oncology clinics in Trinidad		Cross sectional survey at two specialty treatment centers.	Soursop (<i>Annona muricata</i> L.) was the most popular; with 80.7 % usage among 150 patients. Leaves, bark, fruit and seed were reported to be used on a regular basis.	The survey unearthed the most common herbal remedies and functional foods used among cancer patients. Despite the lack of evidence, patients still believe in the efficacy of these alternative remedies.
[47]	<i>Petroselinum crispum</i> has antioxidant properties, protects against DNA damage and inhibits proliferation and migration of cancer cells.		Two human breast adenocarcinoma cell lines – MCF-7 and MDA-MB-231. The extract was tested for its antiproliferative potential against the cell line using MTT assay. Also, comet assay was used to test its DNA-protective effect.	The dichloromethane extract was more potent antiproliferative activity against MCF-7 and also, DNA protective activity against DNA damage.	The antiproliferative potential of the extract against breast cancer cell lines may be due to its strong antioxidant potential. Therefore, it is an important functional food.

Table 3. Summary of articles in this review: Hepatocellular cancer

Author	Title	Functional Food Component	Methods	Results	Conclusion
[48]	Bioactivity evaluation of a novel formulated curcumin	Curcumin	Cultured HCC cell lines were treated with curcumin and the formulated curcumin at different concentrations for proliferation and viability test.	Curcumin and the formulated curcumin were effective in inducing apoptosis through mitochondria dysfunction and also decreasing proliferation and viability of HCC cell lines in a dose-dependent manner.	Formulated curcumin has the same anticancer activity as the conventional curcumin.
[49]	Characterization and inception of a triterpenoid astrakurkurool, as a cytotoxic molecule on human hepatocellular carcinoma cells, Hep3B	Astrakurkurool	Isolated and purified astrakurkurool from the basidiocarp of <i>Astraeus hygrometricus</i> was treated with cell Hep3B in a WST-1 cell proliferation assay followed by cell survival, apoptosis assay etc.	Significant decrease in Hep3B cell viability and induction of apoptosis suggested by DNA fragmentation, nuclear shrinkage and imbalance of cell cycle distribution	Astrakurkurool, a triterpenoid is a natural source for a safer cytotoxic drug against hepatocellular carcinoma.
[50]	2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone induced apoptosis and G1 cell cycle arrest through PI3K/AKT pathway in BEL-7402/5-FU cells	2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC)	HCC multi-drug resistant cell line BEL-7402/5-FU was cultured, DMC was isolated and purified by HPLC. Cells were seeded and treated with DMC using MTT technique to assay for cell viability. ROS level was measured and apoptosis determined.	Induction of apoptosis predominantly via the mitochondria-dependent pathway, induction of cell cycle arrest at G1 and enhancement and generation of reactive oxygen species (ROS)	DMC mediated apoptosis and arrest of G1 cell cycle phase, this presents it as a potential natural therapeutic agent against HCC.
[51]	Quercetin inhibits growth of hepatocellular carcinoma by apoptosis induction in part via autophagy stimulation in mice	Quercetin (QCT)	The effect of QCT on human hepatoma cell lines SMMC7721 and HepG2, cell growth was determined by using the CCK-8 assay followed by cell apoptosis analysis by flow cytometry, western blot for protein determination and in vivo animal studies.	Inhibition of growth of human HCC cells in dose- and time-dependent manner, increase in both autophagosomes and autolysosomes in HCC cell and stimulation of autophagy	Autophagy stimulation may be an important mechanism by which Quercetin and other functional foods induce cancer cell apoptosis.
[52]	Licochalcone A from licorice root, an inhibitor of human hepatoma cell growth via induction of cell apoptosis and cell cycle arrest.	Licochalcone A (LCA)	Extraction of licorice root with ethanol followed by purification of LCA then testing the effect on cancer cell apoptosis.	LCA inhibited the proliferation of HepG2 cells significantly, affecting its growth by terminating cell cycle at G2/M transition.	This research helps us in recognizing LCA as a promising candidate for induction of apoptosis in human hepatoma carcinoma cells.
[53]	Ginger polysaccharides induced cell cycle arrest and apoptosis in human hepatocellular carcinoma HepG2 cells	Ginger polysaccharide (GP)	Extraction of pure ginger polysaccharide, and treatment with cultured HepG2 cells in MTT assay for measurement of cell viability. Hoechst 33258 apoptosis detection kit was used to measure apoptotic nuclear morphology followed by flow cytometry.	GP had significant antitumor effect against HCC, flow cytometry suggested that GP promotes apoptosis and arrest cell cycle in G0-G1 phase.	GP can provide low-cost anti-cancer drug and become a significant functional food.
[54]	<i>Antrodia cinnamomea</i> boosts the anti-tumour activity of sorafenib in xenograft models of human hepatocellular carcinoma	<i>Extract of Antrodia cinnamomea</i> (EAC)	Cultivation of <i>A. cinnamomea</i> and seeding in M25 medium followed by extraction and purification of active compound by HPLC. MTT assay was used to assess the effect of sorafenib and EAC on liver cancer cell viability.	EAC dose-dependently sensitized HepG2 cells to sorafenib-induced cell death mediated through targeting MAP kinases, modulating cyclin proteins expression and inhibiting cancer cell invasion.	EAC can boost the activity of sorafenib on HCC cells. However, more <i>in vivo</i> investigation is needed before the EAC/Sorafenib combination assume clinical application.

Author	Title	Functional Food Component	Methods	Results	Conclusion
[55]	Sesamol Induces Human Hepatocellular Carcinoma Cells Apoptosis by Impairing Mitochondrial Function and Suppressing Autophagy	Sesamol	HepG2 cells were cultured, seeded and incubated in the presence or absence of various concentrations of sesamol for 24 h to observe the colony formation.	Suppression of colony formation, arresting cell cycle at S phase, inducing apoptosis and loss of mitochondrial membrane potential.	Sesamol is a nutritional phenolic antioxidant compound which is an effective inducer of apoptosis by impairing mitochondria in hepatocellular carcinoma <i>in vitro</i> and <i>in vivo</i>
[56]	<i>Athyrium multidentatum</i> (Doll.) Ching extract induce apoptosis via mitochondrial dysfunction and oxidative stress in HepG2 cells	Chlorogenic acid	Collection of <i>Athyrium multidentatum</i> Ching (AMC) and extraction/purification of bioactive compounds, Hep G2 and HL7702 Cell viability was determined using the MTT assay.	Inhibition of cell growth, induction of apoptosis through intrinsic and extrinsic pathways and cell cycle arrest in HepG2 cells	The study provides a new option for the diet of hepatocellular carcinoma susceptible patients.
[57]	Preparation of <i>Prunella vulgaris</i> polysaccharide-zinc complex and its antiproliferative activity in HepG2 cells	<i>Prunella vulgaris</i> polysaccharide-zinc complex (P1-Zn)	Extraction and purification of extract from <i>P. vulgaris</i> . MTT assay for cell viability in HepG2 cell lines followed by flow cytometry, caspase assay e.t.c	Inhibition of proliferation of HepG2 cells at 98.4% inhibition rate at 500 µg/mL through induction of apoptosis (activation of caspase-3 and -9 and mitochondrial dysfunction)	P1-Zn may be a potent candidate for human hepatocellular carcinoma prevention and treatment in the field of functional foods
[58]	Antioxidant and Antitumor Activities of the Extracts from Chinese Yam (<i>Dioscorea oppositifolia</i> Thunb.) Flesh and Peel and the Effective Compounds	Gallic acid, chlorogenic acid, vanillic acid, syringic acid, epicatechin, p-coumaric acid, phlorizin, ferulic acid, rutin, quercetin and kaempferol	Kunming mice were injected with tumor cells of H22. Extract solution of peel and flesh was given to mice and anti-tumor capacity was assayed.	Water and ethanol extracts isolated from Chinese yam (<i>Dioscorea oppositifolia</i> Thunb.) flesh (CYF) and peel (CYP) has antitumor property against hepatocarcinoma tumor (H22) model	Functional food components have been acknowledged as an important determinant in cancer prevention. Studies should focus on studying the specific mechanism exerted by each bioactive component
[59]	Antioxidant and <i>in vitro</i> anticancer activities of phenolics isolated from sugar beet molasses	Gallic acid, cyanidin-3-O-glucoside chloride (CGC) and epicatechin.	Extraction of sugar beet molasses followed by identification and purification of active components using HPLC and spectrometry techniques. Anti-tumor activity against hepatocellular (HepG2) done using MTT assay.	Inhibitory activity against hepatocellular (HepG2) cell lines.	SBM as a strong anti-tumor can be helpful in preparing functional foods against hepatocellular carcinoma.
[60]	Involvement of autophagy induction in penta-1,2,3,4,6-O-galloyl-β-D-glucose-like growth arrest in human cancer cells	Penta-1,2,3,4,6-O-galloyl-β-D-glucose (PGG)	PGG was prepared through acidic methanolysis of tannic acid after which purity was established. hepG2 cells were treated with 25 µM PGG, seeded and cultured to evaluate the proliferative capacity.	Induction of autophagy and senescence <i>in vitro</i> in HepG2 and <i>in vivo</i> in a xenograft mouse model of human HepG2 liver cancer.	PGG is a chemopreventive polyphenolic compound, effective against hepatocellular and other forms of human cancers.

Table 4. Anticancer Mechanism of Functional Food Components in Cervical Cancer

Foods, Plant crude extracts, Fruits, Natural Products, etc.	Compounds	Anti-cancer Mechanism	References
<i>Lycium barbarum fruit</i>	Arabinogalactan	<ul style="list-style-type: none"> • Induction of apoptosis. • Downregulation of Bcl-2/Bax expression. • Upregulation of Caspase-3, 8 and 9. • Cell cycle arrest at G₀/G₁ phase. • ROS generation. • Activation of MAP Kinase signaling shunt. 	[25]
<i>Lycium barbarum fruit</i>	Lycium barbarum Polysaccharide (LBP)	<ul style="list-style-type: none"> • Cell cycle arrest at S-phase. • Increase in intracellular Ca²⁺ ion. • Induction of apoptosis. 	[36]
<i>Polygonatum sibiricum</i>	Methyl Protodioscin	<ul style="list-style-type: none"> • Alteration of cell morphology with pseudopod extension. • Cell cycle arrest at G₂/M phase. • Induce apoptosis. 	[26]
Dietary Phytosterol Ingredients	β-sitosterol	<ul style="list-style-type: none"> • Cell cycle arrest at S and G₂/M phase. • Induction of apoptosis. 	[27]
<i>Salvia miltiorrhiza burge</i>	15,16-Dihydrotanshinone	<ul style="list-style-type: none"> • Regulation of TNF-α expression. • Cell cycle arrest at G₂/M phase. 	[28]
<i>Artemisia herba alba</i>	Caffeoylquinic acid and sesquiterpene lactone	<ul style="list-style-type: none"> • Production of ROS. • Induction of apoptosis. 	[29]
Mulberry	Morin	<ul style="list-style-type: none"> • Alteration of cell morphology. • Induction of apoptosis. • Upregulation of p53, p21 and Wee1 expressions. • Downregulation of CDK1, Cdc25c, surviving, cyclin B1, CHK2. • Cell cycle arrest. 	[30]
<i>Citrus grandis leaf</i>	Isosensetin, sinensetin, tetramethyl-O-isoscutellarein, nobiletin, tangeretin and 5-hydroxy-6,7,8,3',4'-pentamethoxyflavone	<ul style="list-style-type: none"> • Apoptosis. • Diminished expression of anti-apoptotic Bcl-2. • Proteolytic activation of caspase cascade. • Destruction of PARP. 	[38]
Hazelnut shell	neolignans, lawsonicin, cedrusin, balanophonin, gallic acid, phenolic derivatives, dihydroconiferyl alcohol, veratric acid, vanillic acid and carpinontriol	<ul style="list-style-type: none"> • Activation of caspase-3. • Induction of apoptosis 	[32]
Wheat	Caffeic acid, vanillic acid, syringic acid, ferulic acid and coumaric		[80]
Red rice bran Ginger	Proanthocyanin. poly-phenols and flavones- flavanols	Cytotoxicity <ul style="list-style-type: none"> • Apoptosis • Disruption of microtubular network. • Alteration of cell morphology. • Cell cycle arrest at sub G₀/G₁. 	[35,37]

Table 5. Anticancer Mechanism of Functional Food Components in Breast Cancer

Foods, Plant crude extracts, Fruits, Natural Products, etc.	Compounds	Anti-cancer Mechanism	References
Dwarf lilyturf tuber	Dwarf-lillyturf tuber monomer-13 (DT-13)	<ul style="list-style-type: none"> • Inhibition of Tumour Metastasis. • Restriction of cell polarity. • Regulation of Hypoxia dependent cell migration. 	[39]
Diary product; Butter	c9,t11-conjugated linoleic acid (CLA)	<ul style="list-style-type: none"> • Downregulation of ER, PR hormonal receptors. • Inhibition of cell proliferation. • Pro-apoptotic effect. • Activation of Caspase 3 and 9. 	[40]
<i>Lycium barbarum</i> fruit	Arabinogalactan	<ul style="list-style-type: none"> • Cell cycle arrest at Go/G1 phase. • Upregulation of Caspase-3,8 and 9. • ROS generation. • Downregulation of Bcl-2/Bax expression. • Activation of MAP Kinase signaling pathway 	[25]
Soy bean	Genistein	<ul style="list-style-type: none"> • Down-regulation of GPR30 expression. • Inhibition of Akt phosphorylation. • Reduced expression of cyclin D1. 	[41]
<i>Syzygium aromaticum</i>	Phenolic acid, flavonol glucoside, tannins and phenolic volatile oils	<ul style="list-style-type: none"> • Pro-apoptotic effect. • Upregulation of p53, Caspase-3 and 7. • Altered mitochondrial potential. • . Downregulation of expression of Bcl-2, COX-2, cMyc and H-ras. 	[44]
Red pitaya (<i>Hylocereus polyrhizus</i>)	Anthocyanin	<ul style="list-style-type: none"> • Suppressed expression of BRCA1, BRCA2, PRAB, and Erα. • Induction of apoptosis. • Increase in G0/G1 phase • Decrease in G2/M phase. 	[45]
<i>Petroselinum crispum</i>	Crude extract	<ul style="list-style-type: none"> • Inhibition of cell migration. • Protection against DNA damage. 	[47]

Table 6. Anticancer Mechanism of Functional Food Components in Hepatocarcinoma

Foods, Plant crude extracts, Fruits, Natural Products, etc.	Compounds	Anti-cancer Mechanism	References
<i>Curcuma long.</i>	Curcumin	<ul style="list-style-type: none"> • Induction of apoptosis. • Activation of Caspase-3 • Inhibition of NF-κB. 	[48]
<i>Astraeus hygrometricus</i>	Astrakurkurol	<ul style="list-style-type: none"> • Cell cycle at the G0/G1 phase • Induction of Apoptosis • Activation of caspase-8 and Fas protein • Inhibition Akt and NF-κB pathway 	[49]
<i>Cleistocalyx operculatus</i>	2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC)	<ul style="list-style-type: none"> • Cell cycle arrest at G1 • Down-regulation of CDK4 and cyclin D • Up-regulation of Bad and Bax • Decrease expression of Bcl-2 and Bcl-xL • Suppression of PI3K/AKT signaling axis 	[50]
<i>Glycyrrhiza inflata</i>	Licochalcone A	<ul style="list-style-type: none"> • Increase mRNA expression of DR3, DR5, caspases-3, 8 and 9, Fas, Bad, Bax and BCL-2. • Cell cycle arrest at G2/M transition 	[52]
	Quercetin	<ul style="list-style-type: none"> • Induction of autophagy • Inhibition of AKT/mTOR pathway • Activation of MAPK pathway 	[51]
<i>Athyrium multidentatum</i>	Chlorogenic acid	<ul style="list-style-type: none"> • Induction of Apoptosis • Modulation of NFκB, MAPK/ERK and PI3K/Akt pathways 	[56]
Ginger rhizomes, <i>Zingiber officinale</i> Roscoe	Ginger polysaccharide	<ul style="list-style-type: none"> • Induction of Apoptosis • Cell cycle arrest at the G0-G1 phase • Increase expression of Bax, Fas, p53, and caspase-3 • Decrease expression of Bcl-2 	[53]
<i>Sesame seed</i>	Sesamol	<ul style="list-style-type: none"> • Induction of Apoptosis • Suppression of colony formation • Cell cycle at S phase 	[55]
<i>Prunella vulgaris</i>	<i>Prunella vulgaris</i> polysaccharide-zinc complex	<ul style="list-style-type: none"> • Induction of Apoptosis • Activation of caspase-3 and caspase-9 	[57]
<i>Antrodia cinnamomea</i>	Methyl antcinatate B, Dehydroeburicoic acid, 15α-acetyl dehydrosulphurenic acid, Zhankuic acid C and Antcin A, C and K	<ul style="list-style-type: none"> • Mediation of cell death • MAP kinase pathway activation • Modulation of cyclin proteins expression 	[54]
<i>Dioscorea opposita</i> Thunb. (Chinese yam)	gallic acid, chlorogenic acid, vanillic acid, epicatechin, coumaric acid, phlorizin, ferulic acid, rutin, quercetin and kaempferol.		[58]
sugar beet molasses (SBM)	Gallic acid, cyanidin-3-O-glucoside chloride (CGC) and epicatechin.		[59]

4.0 DISCUSSION

Cancer is a disease of ageing that remains a significant cause of death globally in rank following cardiovascular disease [62]. Deaths resulting from various types of cancer continue to rise. In the United States, the American Cancer Society had estimated 13,800, 42,810 and 279,100 new cases of cervical, liver, and breast cancer respectively with an estimated 4,290, 30,160 and 42,690 deaths resulting from cervical, liver, and breast cancer respectively [63]. Therefore, there is an increasing need to curtail the malady: cancer that is ravaging all age groups, genders, and race of the global populace. However, the current therapeutic strategy is challenged by multiple organ toxicity [62] and such low efficacy of drugs led to the discovery of natural compounds with the ability to prevent and manage cancer [64].

4.1 Functional Food and Cervical Cancer: In this review, there are about thirty (30) compounds or classes of compounds reported to actively hamper growth in human cervical cell models. These compounds are functional food components found in plant products.

4.1.1 Arabinogalactan: Arabinogalactan is a potent immunomodulatory agent. In this review, Gong et al [26] reportedly purified this compound from *Lycium barbarum fruit*. It was reported to be the most potent anti-tumor agent among the 3 polysaccharide fractions (LBGP-I-3) purified in the same study. Arabinogalactan repressed growth in human cervical cancer with 55.94% cell viability following MTT assay at 800ug/ml in 24hrs treatment. The anti-cancer mechanism is linked to the ability of arabinogalactan to induce apoptosis by downregulating the expression of Bcl-2/Bax and upregulating Caspase-3, 8, and 9. Disruption of the heterodimeric Bcl-2/Bax is critical to the release of cytochrome c and this represents a significant event in

apoptosis [65]. Therefore, the ability of arabinogalactan to downregulate Bcl-2/Bax is a probable mechanism that punctuates its anti-proliferative potential in cervical HeLa cells, although this compound was also shown to induce cell cycle arrest at G₀/G₁ phase, ROS generation, and activation of MAP Kinase signaling shunt [26].

Other than arabinogalactan, other functional foods have been isolated from the Chinese medicinal herb *Lycium barbarum fruit* with effective anti-cancer properties. For instance, the isolation of *Lycium barbarum Polysaccharide (LBP)* has been reported. Our data showed that this compound can also inhibit the proliferation of HeLa cells. In fact, data from cytometric analysis indicated that LBP disrupts cell cycle progression at S-phase. In the same study, there was an increase in intracellular Ca²⁺ ions, this put together with the ability of LBP to induce apoptosis may underline its anti-tumor potential [37].

4.1.2 Methyl Protodioscin (MPD): Methyl Protodioscin is enriched with high content saponin from the rhizome of *Polygonatum sibiricum*. Data from Ma and colleagues [27] showed that MPD hampered proliferation in the human cervical cancer cell line with altered morphology – pseudopod extension. The anti-cancer capacity of MPD was correlated to its ability to arrest cell cycle progression at G₂/M phase and induce apoptosis via the death receptor pathway [27].

4.1.3 Phytosterol: β-sitosterol, campesterol, and stigmasterol are phytosterols. These compounds are common plant bioactive food components in diets [66-67]. In this review, Alvarez-Sala et al [28] reported the effect of oil enriched with β-sitosterol on HeLa cell. This study demonstrated that β-sitosterol, induces cell cycle

arrest at S and G₂/M phase and decreases cell viability via induction of apoptosis [28].

4.1.4 15,16-Dihydrotanshinone (DI): The traditional Asian functional food *Salvia miltiorrhiza* Burge is enriched with DI and usually well distributed in the root of this plant. Studies have shown that DI repressed cell proliferation in cervical HeLa cells by regulating TNF- α expression [68]; although there is limitation to the anti-cancer activity of DI due to its low solubility in aqueous medium [69]. In recent times, the solubility of DI has been enhanced by liposomes, cyclodextrin inclusion, microemulsion, and nanoparticles [68,71-73]. Furthermore, the research demonstrated that the anti-tumor ability of DI can be improved by copolymer encapsulation. This study encapsulates DI with polylactic-co-glycolic acid activated by polyethylene glycol (PPA) and PPA-conjugated biotin (BPA). The capsules were biophysically distributed by conjugation to nanoparticles. The DI-BPA-NPs polymer repressed cell growth in human cervical cancer cells through the arrest of cell cycle progression at G₂/M phase [29].

4.1.5 Ethyl acetate Fraction (EAF) of *Artemisia herba alba*: LC-ESI-TOF-MS and GC-EI-MS profiling of *Artemisia herba alba* unveiled the presence of numerous bioactive compounds. Bourgou and colleagues reported that the EAF is effective against cell proliferation in HeLa cell [30]. This is primarily due to the presence of cytotoxic compounds in EAF including caffeoylquinic acid derivatives such as di and tri-caffeoylquinic acid, naphthoquinone derivatives [74], and santonin – a sesquiterpene lactone [75]. The mechanism of EAF anti-cancer activity is through the production of ROS and the induction of apoptosis via the mitochondria dependent pathway [30].

4.1.6 Morin : Many fruits and medicinal herbs contain the flavonoid morin [76]. Activity reports showed that morin is an effective anti-cancer agent in breast cancer, oral tumour, colon, and liver cancers [31,77-80]. In human cervical cancer cells, morin altered cell morphology and markedly diminished survival rate by inducing programmed cell death through the death receptor pathway. Also, in the same study, morin treatment incited the sustained expression of p53, p21 and Wee1 and caused the downregulation of CDK1, Cdc25c, survivin, cyclin B1, and CHK2 thereby culminating in cell cycle halt [31].

4.1.7 Citrus grandis Leaf Extract: The chloroform fraction of *Citrus grandis* leaf extract strongly reduces cell viability in human cervical cancer cells via apoptosis. The major apoptotic mechanism elicited is by the ability of the extract to diminish the expression of anti-apoptotic Bcl-2 and subsequent proteolytic activation of caspase cascade, thus leading to the destruction of poly (ADP-ribose) polymerase (PARP). Chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) has revealed the bioactive component of the leaf extract, and this includes: isosensetin, sensetin, tetramethyl-O-isoscutellarein, nobiletin, tangeretin and 5-hydroxy-6,7,8,3',4'-pentamethoxyflavone [39].

4.1.8 Others: There are several other natural sources abundantly replenished with functional food components that are anticancer agents. In this review, we present the work of Esposito and his colleague on Hazelnut shell extract (HSE) [33]. They found out that this extract contains neolignans, lawsonicin, cedrusin, balanophonin, gallic acid, phenolic derivatives, dihydroconiferyl alcohol, veratric acid, vanillic acid, and carpinontriol. These bioactive ingredients are reported to be responsible for the ability of HSE to hamper cell

growth via caspase-3 mediated induction of apoptosis. In another study, the presence of flavonoids and phenolics has been tentatively correlated to inhibition of cell proliferation in HeLa cells [34]. A particular report adumbrated the presence of caffeic acid, vanillic acid, syringic acid, ferulic acid, and coumaric acid in wheat and showed that these bioactive compounds are responsible for the anti-tumor action of wheat [81].

A comparative study of the chemical composition and bioactive properties of *Ganoderma lucidum* from two sources – Serbia; China – revealed that *Ganoderma lucidum* cultivated in Serbia exhibit anti-tumor effect in HeLa cells [35]. In another comparative study, HPLC-PDA aided isolation, punctuating the relative abundance of phenolics, anthocyanin, and proanthocyanin content in brown, purple, and red rice brans. The same study identified the abundance of proanthocyanin in red rice bran and showed that such high amounts may be responsible for its anticancer property [36].

The ability of many functional foods to alter cell morphology has been correlated to the presence of active component capable of disrupting network of microtubules in cancer cells. The Folin-Ciocalteu assay revealed the presence of polyphenols and flavones-flavanols in ginger aqueous extract. The extract disrupted microtubular network leading to altered cell morphology and cell cycle arrest – sub G_0/G_1 – in cervical HeLa cells [38]. Table 4 below shows the overall mechanisms of functional food components in cervical cancer.

4.2 Functional Food and Breast Cancer

4.2.1 Dwarf-lilyturf tuber monomer-13 (DT-13):

Metastasis is one of the established hallmarks of cancer. The features of the tumor microenvironment are complex and interrelated. Dwarf-lilyturf tuber monomer-13 (DT-13) possesses good potential against tumour microenvironment [40]. DT-13 is a saponin monomer

extracted from dwarf lilyturf tuber, a member of subfamily *Radix ophiopogonis* which had been in use for centuries in Traditional Chinese Medicine (TCM). Previous studies have shown that DT-13 exerted remarkable effects on cancer cell migration, invasion, and metastasis [82-83]. In the work of Gao et al. [40], the anti-carcinogenic mechanism of DT-13 encompassed the inhibition of tumor metastasis *in vitro* via increasing expression of non-muscle myosin II-A (NMII-A) and its localization around the nucleus thus restricting its effect on the cell polarity [84]. Moreover, this has been closely associated with ERK/RAF/FAK/Paxillin signaling pathways *in vitro*. It was concluded from this study that DT-13 targeted NMII-A for the regulation of hypoxia-dependent cell migration through RAF, ERK, FAK and Paxillin signaling pathway.

4.2.2 c9, t11-conjugated linoleic acid (CLA):

Dietary sources of functional chemicals are also an explored area of interest to elucidate their anti-cancer properties. Conjugated linoleic acid (CLA) obtained from butter is the isomer of linoleic acid with conjugated double bonds. It has attracted scientific interest because of its anticancer, anti-obesity, and antiaging bioactivities [85-87]. CLA is naturally present in ruminant-derived products, such as milk, dairy, and beef products [87-88].

The mechanism of the anticancer effect of c9, t11-CLA involves reducing breast cancer progression by affecting the level of hormonal receptor and cell proliferation. Tang et al [41] has confirmed the preventive effect of the dietary c9, t11-CLA from butter against breast cancer *in vivo*. It was found that pretreatment with c9,t11-CLA reduced the body weight significantly and reduced the tumor incidence to 50% as well as tumor weight and volume in 7,12-dimethylbenz(α)anthracene-induced mammary cancer. Previous studies have demonstrated that c9,t11-CLA has inhibitory and pro-apoptotic effects on MCF-7 breast

cancer cells *in vitro* (90). Furthermore, Tang et al [41] found that the *c9,t11*-CLA enriched from butter substantially demonstrated a preventive effect against breast cancer *in vivo*. However, the *c9,t11*-CLA enriched in their study contains a lot of other PUFA, which may affect the prophylactic capacity against cancer. Another mechanism shown is that dietary *c9,t11*-CLA can significantly downregulate the hormonal receptor and has anti-proliferative effect against mammary cancer *in vivo*.

4.2.3 Arabinogalactan: Natural compounds with high efficacy, low toxicity, and minimal side effects attract the interest of researchers to explore *Lycium barbarum*, which belongs to the plant family Solanaceae, and it is a traditional medicine and food plant in China. *L. barbarum* fruit exhibits a variety of health-promoting activities including immunomodulation, anti-aging activity, anti-fatigue activity, anti-inflammatory activity, and inhibition of cancer cell growth [60, 91-92]. The underlying anticancer mechanism reported by Gong et al [26] suggested that LBGP-I-3 inhibited the growth of breast cancer cells by cell cycle arrest at the G_0/G_1 phase as well as altered mitochondrial potential.

4.2.4 Genistein: Studies have shown that the consumption of soy foods lowers the risk of breast cancer. Genistein is one of the most abundant isoflavones present in soybeans. It has a chemo preventive effect on mammary carcinogenesis [93-94]. The estrogen receptor (ER) whose alteration induced mammary cancer has been shown to be the target of genistein. This compound antagonizes ER to exert its anti-carcinogenic and chemopreventive properties. In other studies, genistein was reported to block G_2/M progression of the cancer cell cycle (95,96). Zeng et al [41] reported that the anticancer mechanism of genistein against *BRCA1*-silenced breast cancer cells resulted in the

down-regulation of G protein-coupled receptor 30 (GPR30) expression and the inhibition of Akt phosphorylation as well as reduced cell viability, migration, and colony formation.

Chemoprevention was achieved by genistein through the inhibition of the growth and proliferation of Triple Negative Breast Cancer (TNBC) cells with mutant *BRCA1* by targeting GPR30 via GPR30-Akt signaling, resulting in aggressiveness of TNBC cells. This led to the reduced expression of Akt, and subsequently cyclin B1, a key enzyme involved in cell cycle progression in the G_2/M phase. Furthermore, *BRCA1*-mutant breast cancer cells exhibited higher levels of intracellular ROS than those in the wild-type cells. Genistein treatment lowered the ROS levels through up-regulation of Nrf2 signaling.

4.2.5 Mungbean Vicilin Protein (MBVP): Functional foods are known to exert beneficial effects on human health in numerous ways. The natural plant-based principles are being explored as relatively more effective, safer and cost-effective preparations [97].

Mungbean (*Vigna radiata*) is one of the popular foods in India because of being a rich protein source. In a particular study, mungbean vicilin protein (MBVP), a hydrolysate was generated upon enzyme treatment alongside two other hydrolysates [43]. Vicilin is a major seed storage protein and contains bioactive peptides. Anti-proliferative activity of mungbean seed extracts and their hydrolysate on breast cancer cells MCF-7 and MDA-MB-231 showed that among other hydrolysate, the MBVP showed significant anti-proliferative activity against both MCF-7 and MDA-MB-231 breast cancer cells at the doses between 0.2–1.0 mg/ml. It was fascinating that, MBVP showed significant dose dependent anti-proliferative effect against both cancer cells, with 50%

inhibition observed after treating cells with 1mg/ml of MBVP after 48 hrs.

4.2.6 Soy Isoflavone: Uifălean et al [44] used a global metabolomic study to compare the metabolome of two different breast cancer cell lines, MCF-7 and MDA-MB-231, in response to studies on three soy isoflavones: genistein (Gen), daidzein (Dai) and a soy seed extract (Ext). Metabolomic study was carried out because isoflavones have different binding capacities and potencies [98]. A dose dependent effect was observed at high isoflavone doses (IC₂₀) and anti-proliferative effects were seen on exposed MCF-7 and MDA-MB-231 cells. However, low isoflavone doses (SC₂₀) induced estrogen-like effects by stimulating the cell proliferation of MCF-7 cells. Therefore, utilizing the correct dose and elucidating the multiple molecular mechanisms of isoflavones may be a powerful tool in mammary cancer chemoprevention and highlights how some foods may cause cancers to become worse.

4.2.7 Phenolic acid, flavonol glucoside, tannins and phenolic volatile oils: Lately, epidemiological studies reveal that long-term consumption of plant-derived functional foods is associated with a lower risk of breast carcinoma [99-101]. Dried flower buds of cloves (CLOs). CLOs (*Syzygium aromaticum* L.) are spices, which consist of a mixture of phytochemicals such as acids, flavonol, glucosides, tannins, and phenolic volatile oils. It has anti-proliferative, anti-inflammatory, antibacterial, and antiseptic activities, which make this food a potentially suitable natural substance for cancer chemoprevention [102]. In a particular study, it was reported that CLO significantly inhibited the risk of mammary gland carcinomas in rats in a dose-dependent manner [45]. Differential doses of dietary administered CLO significantly decreased tumor frequency by 58.5% and 47.5% respectively compared to control rats.

4.2.8 Petroselinum crispum extract: The chemical composition and pharmacological properties of *P. crispum* have been previously reported in various studies. The herb contains flavonol glycosides of quercetin, apiol, myristicin, luteolin, terpenes, phthalides, furanocoumarins, apiin, carotenoids, ascorbic acid, and tocopherol [103-104]. It was reported that the dichloromethane extract of *P. crispum* leaves and stems showed antioxidant activities, inhibition of proliferation and cell migration in MCF-7 cells. The extract also protected against DNA damage induced by H₂O₂. Further, mouse fibroblasts (3T3-L1) pre-treated with 400 mL⁻¹ of the extract showed 50.9% protection against H₂O₂-induced DNA damage, suggesting its potential in cancer prevention. The extract (300 extract mL⁻¹) inhibited H₂O₂-induced MCF-7 cell migration by 41% ± 4%. Thus, since cell migration is necessary for metastasis of cancer cells, inhibition of migration is an indication that *P. crispum* extract has the potential to hamper metastasis and prevent cancer progression. Table 5 below shows the overall mechanisms of functional food components in breast cancer

4.3 Functional Food and Hepatocarcinoma

4.3.1 Curcumin: Curcumin has been used widely as a functional food because of its pharmacological properties including its strong anticancer properties. It is a polyphenolic compound extracted from rhizomes of *Curcuma longa*, a plant which has been found to have strong antioxidant and anti-inflammatory effects [105-106]. Liao et al [49] formulated curcumin pellets using solid dispersion techniques due to the limitations in the oral usage of curcumin as a food supplement because of its poor oral bioavailability. The biological functions of formulated curcumin were tested using C-Map and Library of Integrated Network-Based Cellular Signatures (LINCS) Unified Environment (CLUE) gene expression database. Formulated curcumin and the conventional type significantly inhibited HCC cell lines Huh7, Mahlavu, and PLC5 in MTT assay. In addition, conventional and formulated curcumin separately induced apoptosis by activating caspase-3 and potently inhibited NF-κB.

Finally, the formulated curcumin has an increased oral bioavailability in animal models.

4.3.2 Astrakurkurol: Astrakurkurol, a triterpenoid extracted from fresh basidiocarps of the edible mushroom *Astraeus hygrometricus* was found to have anti-proliferative properties [50]. *Astraeus hygrometricus* has various health benefits such as anticancer, antidiabetic, and antioxidant properties [107-108]. Nandi and colleagues [50] demonstrated that astrakurkurol can act as a cytotoxic drug. It was found to induce apoptosis in hepatocarcinoma cell line (Hep3B) and arrest cell cycle at the G₀/G₁ phase. Following the establishment of the structural stability of astrakurkurol using single crystal X-ray diffraction study and density functional theory calculations, the compound triggered the activation of caspase-8 and death receptor Fas protein mediated apoptotic events, inhibiting Akt and NF-κB pathway. Terpenoids generally account for a large number of bioactive compounds implicated in the prevention and therapy of various diseases [109].

4.3.3 Chalcones: Functional chalcones are well implicated in natural anti-cancer therapy. In our data, Ji et al [51] reported that 2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC), isolated from the buds of *Cleistocalyx operculatus* inhibit growth in HCC multi-drug resistant cell line BEL-7042/5-FU by triggering apoptosis via induction of cell cycle arrest at G1 achieved by the downregulation of CDK4 and cyclin D as indicated by flow cytometry analysis. DMC persuaded the up-regulation of Bad and Bax and decreased the expression of anti-apoptotic Bcl-2 and Bcl-xL. DMC further increased levels of p53 and inhibited NF-κB nuclear-localization by suppressing PI3K/AKT signaling axis.

Wang et al [53] reported a similar chalcone; Licochalcone A (3-a,adimethylallyl-4,4'-dihydroxy-6-methoxychalcone), LCA, a characteristic chalcone of

licorice, a root of *Glycyrrhiza inflata*. LCA was purified using high-speed counter-current chromatography (HSCCC) technique followed by HPLC then tested with HepG2. Real-time PCR and flow cytometry revealed that the anti-cancer action of LCA involves an increase in mRNA expression of DR3, DR5, caspases-3, 8 and 9, Fas, Bad, Bax, and Bcl-2. Furthermore, LCA exhibits its anti-proliferative effect against HepG2 cells by terminating the cell cycle at G₂/M transition, thus suppressing genes involved in cell cycle progression.

4.3.4 Quercetin: Quercetin is a flavonoid compound present in many plants; its biological activities are related to the presence of five hydroxyl groups on its ring structure [110]. In this review, Ji et al [52] reported that quercetin inhibited the growth of human HCC cells in a dose-dependent manner while ensuring minimal cytotoxicity in normal liver cells. Analysis of autophagy-related biomarkers using western blot and microscopy techniques dictates that quercetin induces autophagy by increasing both autophagosomes and autolysosomes in those cells, inhibiting AKT/mTOR pathway and activating the MAPK pathway. *In vivo* analysis using mice models further demonstrate the anti-tumor property of quercetin, which is associated with autophagy simulation and apoptosis induction as well.

4.3.5 Chlorogenic acid: In the report by Qi et al [57], chlorogenic acid, an active compound found in *Athyrium multidentatum* arrests cell cycle in HepG2 cells; it induces apoptosis through intrinsic and extrinsic pathways, modulating NFκB, MAPK/ERK, and PI3K/Akt pathways [57]. Chlorogenic acid (3-caffeoylquinic acid) is a polyphenol and the ester of caffeic and quinic acid, which is an important functional food in hepatocarcinoma cancer treatment and prevention [111].

4.3.6 Others: In this systematic review, we also established from our data various plant extracts that show effective anti-proliferative potential against hepatocarcinoma cancer cells through diverse mechanisms. Ginger polysaccharide (GP) induced apoptosis in HepG2 cells by arresting cell cycle at the G0-G1 phase [54]. Analysis showed that GP consists of five monosaccharides including L-rhamnose, D-arabinose, D-mannose, D-glucose, and D-galactose in a molar ratio of 3.64: 5.37: 3.04: 61.03: 26.91 respectively. Also, real-time fluorescence quantitative PCR uncovered that GP increases the mRNA expression of Bax, Fas, p53, and caspase-3 with decreased expression of Bcl-2. Liu et al [56] reported that sesamol, extracted from sesame seed, suppressed colony formation, induced apoptosis in HepG2 cells by arresting cell cycle at S phase and caused loss of mitochondrial membrane potential. *Prunella vulgaris* polysaccharide-zinc complex (P1-Zn), a modified polysaccharide extract from *Prunella vulgaris* inhibits proliferation by activation of caspase-3 and -9 thereby inducing apoptosis [58]. In addition, biologically active extracts of *Antrodia cinnamomea* (EAC) sensitize HepG2 cells to sorafenib, thus causing cell death by targeting MAP kinases, modulating cyclin proteins expression, and inhibiting cancer cell invasion. Some of the bioactive compounds in the extract as determined by HPLC include Methyl antcinatate B, Dehydroeburicoic acid, 15 α -acetyl dehydrosulphurenic acid, Zhankuic acid C and Antcin A, C, and K [55]. Lastly, extracts from Chinese Yam (*Dioscorea oppositifolia*) containing compounds such as gallic acid, chlorogenic acid, vanillic acid, and epicatechin also showed antitumor properties against hepatocarcinoma tumor (H22) model in rats [59]. Table 6 below shows the overall mechanisms of functional food components in hepatocarcinoma.

4.4 Overall Mechanism: The chemoprevention and anti-cancer mechanism of Functional Food components (FFc)

has been expatiated in this review. In the graphical summary, one of the anti-cancer mechanisms of FFc is the inhibition of NF- κ B signaling. FFc impairs the translocation of NF- κ B into the nucleus for transcription induction. Therefore, cancer cells whose survival mechanism depends on NF- κ B will be challenged by the effect of FFc. Also, the ability of FFc to inhibit NF- κ B signaling means that the transcriptional target of NF- κ B (TRAF and an inhibitor of caspase-8) will not be induced. This together with the capacity of functional foods to sustain the expression of caspase-8 will therefore increase apoptosis in cancer cells.

TNF- α signaling also promotes apoptosis. TNF- α signaling enables the proteolytic activity of caspase-8 and the activation of upstream kinases that triggers the availability and activation of JNK, whose resultant effect is pivotal to the active role of p53. FFc upregulates the expression of p53 which is a transcriptional factor and a guardian of the genome, and p21 which is the product of p53 transcriptional activities. The activity of p53 can be altered by PI3-Akt signaling, a way by which this is prevented is a close regulation of this shunt. FFc inhibits the PI3-Akt signaling, therefore availing the p53-mediated activities including ROS generation and synthesis of p21. p21 inhibit CDK/Cyclin heterodimers, which leads to cell cycle arrest.

Events that cause mitochondrial membrane permeability to cytochrome c are critical to caspase-9 mediated induction of apoptosis. One of such intra-mitochondrial events is the dimerization of Bax and Bak. Another anti-cancer mechanism of FFc is to upregulate the Bax and caspase-9 to induce apoptosis.

CONCLUSION

In conclusion, functional foods contain active components and or compounds that can serve as anti-tumor agents as a result of their great antioxidant

property [112]. Studies in this review identified diverse plant products with their various screens of bioactive components, which offer prophylactic and curative measures in human cancer cells – cervical, breast, and liver cancers. These properties are related to the presence of antioxidant behavior of these components which enhanced their anti-cancer mechanism [113]. Moreover, the established anti-cancer mechanisms include apoptosis, reinforcement of anchorage dependent growth, inhibition of metastases, tumor microenvironment modification, cell cycle arrest, ROS generation, control of gene expression, and regulation of signaling shunts. Therefore, functional foods exhibit possible tremendous therapeutic capacity against cervical, breast, and liver cancers.

Abbreviations: FFc: Functional Food components, FUFOSE: Functional Food Science in Europe, FOSHU: Foods for Specified Health Use, IARC: International Agency for Research on Cancer, HBV: Hepatitis B virus, HCC: Hepatocellular carcinoma, DT-13: Dwarf-lilyturf Tuber monomer-13, LBP: Lycium barbarum polysaccharide, LBGP-I-3: Arabinogalactan, MBVP: Mungbean Vicilin Protein, DMC: 2',4'-Dihydroxy-6'

methoxy-3',5'-dimethylchalcone, QCT: Quercetin, LCA: Licochalcone A, MPD: Methyl Protodioscin, DI: 15,16-Dihydrtanshinone, EAF: Ethylacetate Fraction, CLA: c9,t11-conjugated linoleic acid, CLO: Syzygium aromaticum, DMC: 2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone, ROS: Reactive Oxygen Species, Gallic acid, CGC: cyanidin-3-O-glucoside chloride, GP: Ginger polysaccharide, P1-Zn: Prunella vulgaris polysaccharide-zinc complex, PGG: Penta-1,2,3,4,6-O-galloyl-β-D-glucose, Non-muscle myosin II-A (NMII-A).

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