A Comprehensive Review of Dietary Factors Involved in Aetiology and Prevention of Cancer

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ABSTRACT

Cancer has emerged as far more common disease than what it was once considered. An alarming increase in the incidence of cancer in recent years is a cause of major concern. Sedentary lifestyle, consumption of processed foods, alcohol, increasingly stressful life and smoking is considered to be contributory factors. Diet among all these factors has close association with the health of an individual. Increasing evidences have associated certain food ingredients and their addictions as risk factors for development of cancer. Similarly, millions of investigations have pointed out the role of specific nutrient in the diet in blocking specific cancer cell growth pathways. Present paper reviews the influence of dietary factors in the aetiology of cancer. It discusses the role of intermediate metabolites released in triggering transformation of cells. The paper further elaborates on the potential of various dietary components in prevention of cancer, improving effectivity of chemotherapy treatment and lowering the risk of long-term complications in cancer patients. This knowledge is important in making decisions regarding both individual's dietary choices and shaping health promoting policies.

Key Words: Chronic, Prevalence, N-nitroso compounds, Dietary, Phytochemical

1. INTRODUCTION

Cancer is a chronic disease encompassing large group of diseases affecting any part of the body.[1] An important characterizing feature of cancer is the rapid creation of abnormal cells.[1] The cancer cells can grow beyond their usual boundaries to invade adjoining parts of the body and spread to other organs.[1] Cancer is a cause of death worldwide leading accounting for nearly 10 million deaths per year.[2] Figure 1 gives the most commonly occurring types of cancer and their incidence worldwide.

An alarming increase in the incidence of cancer in recent years is a cause of major public health concern. In spite the considerable advancements in the field of cancer research, prevention and treatment, a 12% increase in the incidence of cancer is seen every year.[3] Cancers of oral cavity, lungs, colon, breasts and cervix carries the major burden of total cancer cases.^[2] Increasing prevalence of cancer in the younger age group in the recent years adds gravity to the current incidence rate.^[2] One woman dies of cervical cancer every 8 minutes in India. For every two women newly diagnosed with breast cancer, death of one woman is recorded. Mortality due to

tobacco use is estimated to be over 3500 persons every day and it accounts for 3,17,928 deaths in India. It is estimated that India would be witnessing an epidemic of cancer by 2050.[4]

No cancer has a single cause, they all are multifactorial, like diabetes and heart ailments. There are multiple causes behind increase in cancer cases in India. Some are suggested to be adoption of western lifestyle, improper dietary habits, dairy (due to rBGH, FSH, LH in milk production), processed foods, food additives, nonvegetarian diets, chemical pollution and sedentary lifestyle.^[5] According to the American Institute for Cancer Research, poor lifestyle, longer working hours, increasing stressful lives, smoking and alcohol consumption are major contributing factors for the increase in incidence of cancer.^[6]

Cancer is growing worldwide and the patterns of cancer onset are suggestive of

regional lifestyle and environmental influence.^[7] Certain types of cancers have been linked to genetic predisposition.[7] However, the main cause of its occurrence is mostly related to external factors such as life style, environmental toxins and diet.[8] The diet has a primary influence on lifestyle of an individual and is also one of the factors contributing to certain types of cancer.[8] It certainly plays a very valuable role in prevention of cancer and protecting an individual from the harmful effects of cancer treatment.[8] The present review discusses various dietary factors that influence cancer development and prevention. This knowledge is important in making informed decisions regarding both individual dietary choices and shaping of promoting policies. Figure 1 health percentage of estimates the cancer incidences worldwide including both sexes and all ages.

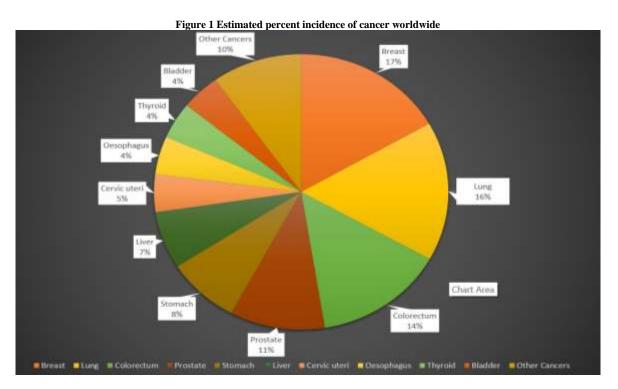


Figure 1 shows the most commonly occurring types of cancer and their incidence worldwide.

2. Role of Diet in the Aetiology of Cancer:

Diet is one of the important modifiable risk factors for cancer. There are number of food ingredients particularly in processed foods that contains a variety of carcinogenic as well as mutagenic agents. It has been stated that certain dietary aspects are linked with

increase in cancer risk. Regular consumption of red and processed meat, alcohol, tobacco, processed and canned foods, sugar sweetened drinks and refined carbohydrates may predispose the risk of transformation in a multistage process that generally progresses from pre- cancerous lesions to a malignant tumor.

2.1 Red and Processed Meat:

According to World Health Organization processed meat includes ham, bacon and

salami are considered as Group 1 carcinogen, which has strong evidence that causes cancer and increases the risk of bowel and stomach cancer while red meat, such as beef, lamb and pork come under the Group 2 carcinogen [9] shown in Figure 2. The current research shows that red and processed meat consist of both natural and added chemicals that causes colorectal cancer.[9]

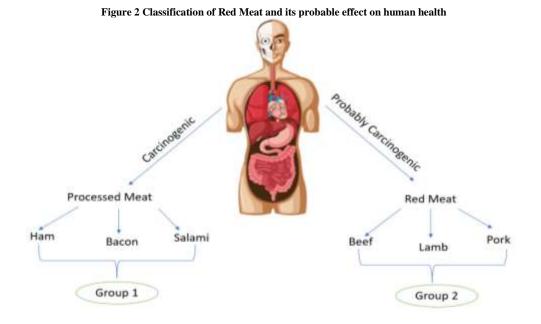


Figure 2: Figure 2 shows the varieties of red and processed meat and probable risk to develop into two categories i.e., Group 1 Carcinogenic and Group 2 Probably Carcinogenic. The proposed biochemical mechanisms by which the genotoxins and components are generated in the red and processed meat and damage the DNA in colorectum is given below and its mechanism can be seen in Figure 3.

Figure 3 Mechanism of DNA damage by red and processed meat.

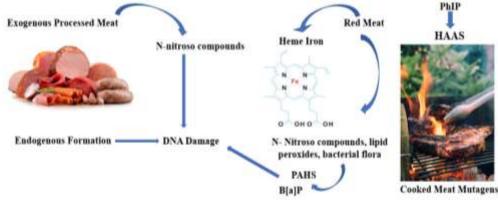


Figure 3: Figure 3 denotes the mechanisms of DNA damage in colorectum by Genotoxicants in red and processed meat

2.1.1 N-nitroso compounds (NOCs):

N-nitroso compounds (NOCs) are formed during processing, storage, or preparation of meat. Nitrite inhibits the growth of bacteria and is therefore often added to meat to preserve it.[10] The reaction of nitrite with degradation products of amino acids results in the formation of NOCs. During the curing of meats, the carcinogenic NOCs formed include N-nitroso dimethylamine (NDMA), N-nitrosodiethylamine, Nnitrosodibutylamine, N-nitrosopyrrolidine, and N-nitrospiperidine.[10] NOCs present in meat undergo metabolic activation by cytochrome P450 2E1 in the gastrointestinal tract.[10] Studies show that endogenously formed NOCs, which become elevated in gastrointestinal the tract following consumption of processed or red meats.[10] endogenous nitrosamines The and nitrosamides, generated by the reaction of nitrite with the products of amino acid's degradation in the stomach, accounts up to 75% of the total NOC exposure.[11] It induces the G-A transitions and G-T transversions that leads to the mutations in cancer driver genes, H-ras and K-ras oncogenes and the p53 tumour suppressor gene, in the gastrointestinal tract.[10] The levels of endogenously produced NOCs in feces of healthy subjects on a fresh or processed red meat diet were ten-fold or greater than those in feces of volunteers on a vegetarian diet.[10] The percentage of colonic exfoliated cells staining positive for NOCs derivate was significantly higher in feces of subjects on the high red meat diet than those consuming a vegetarian diet.[10] Epidemiological and pre- clinical studies have reported a strong linkage between the NOCs and colorectal cancer.[10]

2.1.2Heme Iron:

Heme is abundantly present in red meat. It is poorly absorbed by the small intestine and thus ends up in large intestine i.e., colon.[10] The ingestion of heme iron results in lipid peroxidation and formation of total N- nitroso compounds in the colon.[10] Experimental studies have suggested that heme iron irritates and damages the cells in colon. This may be associated with its redox properties.[10] It undergoes free radical- generating reactions that in turn produces reactive oxygen species (ROS), oxidation of heme iron leads to DNA damage and it is considered highly mutagenic.[10] The supply of hemin leads to cytotoxicity and formation of DNAdamaging agents, and cell proliferation of colonic mucosa of rodents. One of the products of lipid peroxidation is MDA (Malondialdehyde) which is cytotoxic and genotoxic aldehyde.[11] This aldehyde can promote cancer progression, as reported by epidemiological and experimental studies.[11] Thus, lipid peroxidation as thought to be one of the principal mechanisms in the carcinogenicity of red and processed meat induced by heme.^[11]

2.1.3 Polycyclic Aromatic Hydrocarbons:

Polycyclic aromatic hydrocarbons (PAHs) are considered as toxic substances.[11] It is produced by cooking at high temperatures, such as barbecuing, or by the food's processing by using smoking.[11] The PAH (over principal 100 identified) classified by the IARC as potential carcinogenic to human (Group 1) is the benzo[a]pyrene (BaP).[11] It tends to be a genotoxic compound when it is converted to benzo[a]pyrene diol- epoxide (BPDE) by metabolic reactions.[11] It interferes with the bases of DNA, resulting in the DNA damage which is responsible for cancer progression.[11]

2.1.4 Heterocyclic Amines:

Heterocyclic Amines are generated in meat by cooking procedures at high temperature through a specific reaction called Millard reaction.[11] The reaction between free amino acids and sugar takes place resulting information of heterocyclic amines potentially mutagenic for humans.[11] The

Heterocyclic amines found in cooked raw meat are 2-Amino-3, 8-dimethyl imidazo -[4,5 f] quinoxaline (MeIN Qx) and the 2-Amino-1-methyl 6 phenylimidazo [4-5b] pyridine (PhIP). These compounds are classified by IARC as carcinogenic to human.[11] It is seen that Heterocyclic amines undergo metabolic activation to yield mutagen which regulates their carcinogenicity.[11] The levels of these compounds are particularly high after the consumption of cooked meat.[11] The heterocyclic amines bind with DNA and results in formation of DNA adducts.[11] Epidemiological studies have shown a strong association between Heterocyclic amines and colorectal cancer.[11]

2.2 Alcohol consumption:

Alcohol is a psychoactive drug and active ingredient in certain drinks like beer, wine, distilled spirits.^[12] and Its chronic consumption is a major health issue worldwide and may lead to damage of almost every organ of the body.[12] Increasing number of studies, have shown an association of alcohol consumption and with onset of cancers such as liver cancer. breast cancer, upper aerodigestive tract (mouth, oropharynx, hypopharynx, and oesophagus), pancreas and colon.[12]

The International Agency for Research on Cancer (IARC) has listed both ethanol and its major metabolite, acetaldehyde, as a carcinogen in humans.^[12] The mechanism underlying alcohol- induced cancer involves the genotoxic effects of acetaldehyde, increased oestrogen concentration, cellular stress and altered folate metabolism, and inflammation.[12] The metabolism of ethanol amongst all plays an important role carcinogenesis.[12] An international in group of epidemiologists and alcohol researchers from the IARC concluded from the available epidemiological data that the occurrence of malignant tumours of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum, and female breast are related to the consumption of alcoholic beverages and the effect is dose dependant.[12] Ethanol is absorbed by small intestine and is metabolized by alcohol later dehydrogenases (ADH) into acetaldehyde in the liver.[12] High alcohol consumption

catalyses ethanol into acetaldehyde producing reactive oxygen species (ROS).[12] It has been seen that ethanol metabolism imbalance leads to alcoholassociated cancer.[12] Table 1 shows the corelation of alcohol consumption with risk for different type of cancer.

Table 1 Correlation of alcohol consumption with risk for type of cancer.				
Sr.no.	Alcohol Consumption per day	Type of Cancer		
1.	10g of alcohol per day	Breast Cancer		
2.	25g of alcohol per day	Upper aerodigestive tract cancer		
3.	50g of alcohol per day	Colorectal Cancer		
4.	80g of alcohol per day	Hepatocellular carcinoma		
5.	More than 80g of alcohol per day	Pancreatic cancer		

Table 1: Table 1 shows the correlation between the quantity of alcohol consumed per day by an individual with risk of developing specific type of cancer

2.3 Tobacco:

Tobacco is one of the leading causes of progression of cancer and associated deaths. Regular use of tobacco in any form chewing or cigarette smoking have an increased risk of developing various types of cancers due tobacco induced DNA damage.[8] to

Tobacco increases the risk for lung, larynx, mouth, oesophagus, throat, bladder, kidney, liver, stomach, pancreas, colon, rectum, cervix, and acute myeloid leukaemia cancer.^[8] As such there is no safe level of tobacco use. Even if one quits it, regardless of their age and healthy diet they still can develop cancer due to harsh carcinogens present in it.[8] The problems associated with tobacco is the poisons present in it leads to weakening of body's immune system also for people already suffering

from cancer making it harder for them to cells. leading to kill cancer their uncontrollable proliferation.[8] The carcinogens can damage or bring mutations in cellular DNA, is allowing the cell to grow out of control and progress into a tumour.[8] Prevention of tobacco related cancer is to completely stop its usage. It is also important to avoid second-hand usage of tobacco (smoke generated by others).[8] Quitting the use of tobacco can lower the risk of about 12 types of cancer.[2] Withing 5-10 years of quitting the use of tobacco, there is a chance of getting drop in cancer of mouth, throat, or larynx by half while within 10 years of quitting the chance of getting bladder, oesophagus or kidney decreases by half and for also for lung cancer it.[8]

2.4 Processed and Canned Food:

Pre-packaged, processed, and canned foods are typically high in fat, salt, and sugar.[13] An observational study published online by the BMJ showed the risk of consuming prepackaged, processed, and canned foods, by analysing the dietary questionnaire answers of 105,000 middle-aged men and women.[13]

It was seen that they faced certain health issues after consuming such food in high quantities.[13] The foods were grouped according to degree of processing — that is, the amount of change the ingredients go through as food makers improve flavour, colouring, and shelf life.[10] The dehydrated soups, baked goods, sugary cereals, processed meats, biscuits, and sauces were considered ultra-processed foods while the less processed foods included canned vegetables, cheeses, and freshly made unpackaged bread.[13] It has been stated that every 10% increase in consumption of ultra-processed foods was associated with a 12% higher risk for cancer in general and an 11% increased risk for breast cancer.^[13] There was no significant link found to prostate or colorectal cancer.[13] This study although does not prove the direct correlation of ultraprocessed foods with cancer, but the results indirectly signify increase in the risk of cancer.[13]

The International Agency for Research on Cancer (1972-1981) has published 24 monographs, many of which evaluate the carcinogenic risk of selected additives to humans.[13]

2.5 Sugar Sweetened Drinks:

WCRF recommendation states to limit the intake of sugar sweetened drinks such as sodas, sport drinks, energy drinks, coffee, tea, and flavoured syrups.^[14] It has shown that consumption of these drinks can increase the energy intake, which results in weight gain, overweight and obesity.[14] The excessive body weight contributes to an increased risk of various types of cancers pharynx, such as mouth, larynx, stomach, pancreatic, oesophageal, gallbladder, breast. liver, colorectal, ovarian, prostate and kidney.^[14] It shows that sugar sweetened drinks lead to gains in the visceral adiposity, independent of the body weight which in turn promotes tumorigenesis through alterations in adipokine secretion and cell signalling pathways.[14]

Certain sugar related derivatives might also play a role in cancer induction. 4methylimidazole, is a caramel colour additive that is added to drink for colouring purpose. It is potentially carcinogenic as experiments on female and male mice showed an increase in adenomas and carcinomas of the lung in exposed mice relative to controls thus considering it equally carcinogenic for humans as well.[14]

2.6 Sugar and Refined Carbohydrates:

Carbohydrate is an important component of diet that has been hypothesized to modulate cancer risk depending on the amount and type of carbohydrate consumed in the diet.[15] Carbohydrates are broken down into simple sugars in the intestine, where they are absorbed by the blood stream, increasing the blood sugar levels. Eating a lot of simple carbohydrate at once raises

insulin levels quickly.[15] High insulin levels lead to a rapid fall in blood sugar, it is a sort of "rebound" effect where low blood sugar levels signal the body that it is low on fuel which than triggers the appetite, encouraging to consume food again, and to bring blood sugar levels back to the normal.[15] This leads to weight gain, as excess insulin leads to fat storage. The fat gets developed around the abdomen and is metabolically active, slowing the processing of insulin, thus effecting the genetic tendency for insulin resistance. Cancer and Diabetes occur together more often than would be expected.^[15] Consumption of simple sugars, glycaemic index (GI) and glycaemic load (GL), has been hypothesized to increase cancer risk, although findings have been mixed. Makarem et al. analysis of Framingham cohort reported the no significant associations between GI or total carbohydrates and risk of several adiposityrelated cancers.[15]

Simple carbohydrates most probably increase the risk by activating the Insulin-IGF-1 axis and by employing aerobic glycolysis as the primary energy- harvesting pathway.[15] On the other hand, complex carbohydrates reduce the risk by disrupting the Insulin-IGF-1 axis. quenching bioavailable androgenic and estrogenic factors, resulting the increase in the excretion of carcinogens, and modulating gastrointestinal microbiota.^[15] the Different studies have indicated that cancers like breast, prostate, colorectal, head and neck cancers show a relation with the intake of carbohydrates, but it is still unclear to understand.^[15]

3. Dietary Factors in Prevention of Cancer:

Adoption of lifestyle for prevention of cancer far more outweighs all the treatment options and therapies post cancer development. There exists increasing evidence that dietary factors can play important role in the prevention of cancer. High intake of polyphenol/Phyto-oestrogen -rich food (i.e., flavonoids, soya products), as well as fibres, vitamins and proteins, may have potential protective effects against cancer occurrence. Vitamin D supplementation, other vitamins and oligoelements may have protective role in decreasing the risk of cancer. It is worthwhile to prevent it through adherence of certain nutrition that will help in prevention of cancer and maintain healthy state of life.

3.1 Plant-based foods:

Plant-based foods are set to be most primarily used for cancer management. Epidemiological studies have consistently shown that regular consumption of plantbased foods is strongly associated with reduced risk of developing chronic diseases, such as cancer.[16] Plant- based foods are rich in pigments and phytochemicals that antioxidant exhibit strong and antiproliferative activities. The major part of total antioxidant activity is from the combination of phytochemicals.[16] Hence was stated that the additive and it synergistic effects of phytochemicals in plant- based foods are responsible for the potent antioxidant and anticancer activities. [16]

Phytochemicals are defined as bioactive non-nutrient plant compounds in fruits, vegetables, grains, and other plant foods that have been linked to reducing the risk of major chronic diseases.[16] It is estimated that >5000 individual phytochemicals have been identified in fruits, vegetables, and grains, but a large percentage still remain unknown and need to be identified before we can fully understand the health benefits of phytochemicals in whole foods.[16] Phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogencontaining compounds, and organosulfur compounds. The most studied of the phytochemicals are the phenolics and carotenoids.^[16]

Some of the plant- based foods rich in phytochemicals are fruits, vegetables, whole grains, and other plant foods such as herbs

and spices, millets etc that have a role in prevention of cancer.

3.1.1 Fruits:

Among the 11 most commonly consumed fruits, cranberry has the highest total phenolic content, followed by apple, red grape, strawberry, pineapple, banana, peach, lemon, orange, pear, and grapefruit.[16] A major focus of phenolic compounds is the inhibitory effects on the stress-activated NF-KB and AP-1 signal cascades in cancer cells which are regarded as major therapeutic targets. Phenolics can enhance the body's immune system to recognize and destroy cancer cells as well as inhibiting the development of new blood vessels (angiogenesis) that is necessary for tumour growth.[17] They also attenuate adhesiveness and invasiveness of cancer cells thereby reducing their metastatic potential.[17] One of the other most interesting fruit called passion fruit is rich in carotenoids and polyphenols.^[18] Carotenoids such as lycopene and βcarotene have shown an effect on the inhibition of the cell cycle progression and apoptosis induces activity, which is beneficial for the prevention of tumour growth.[18] Beta- carotene and lycopene arrest the cell cycle in which beta carotene causes the arrest of G0/G1 phase in myeloid leukaemia cells at lower concentrations and at higher concentrations leads to arrest of G2/M phase.[18] The seeds of passion fruit abundantly consist of Piceatannol, a stilbene which consist of a variety of biological activities.[18] Piceatannol present in passion fruit seeds prevents high fat diet induced cardiovascular diseases and promotes neural stem cell differentiation to astrocytes.[18] It suppresses the proliferation of cancer cells and several pathways leading to piceatannol-induced apoptosis, the proliferation of cancer cells is supressed by mitochondriamediated intrinsic The edible berries pathway.[19] (like strawberries, cranberry. gooseberry. bayberry, mulberry, red current etc) consumption rodent in exerts

chemoprevention in series of cancer- oral cavity, breast, lung and oesophageal.[20] Berries are notably rich in compounds that shown to exert potential for are chemoprevention and particularly flavopiridol, ellagic acid, anethole and resveratrol have been demonstrated to inhibit the NF- κ B signalling pathway, either at the point of signalling cascade activation or at the point of NF-kB's translocation into the nucleus.^[20] Other points of interference include the DNA binding dimmers and/or interactions with the basal transcriptional machinery.^[20]

3.1.2 Vegetables:

In case of vegetables, Cruciferous vegetable like broccoli, cauliflower, cabbage, brussels sprouts, Bok choy, kale, and pods such as drumsticks, jackfruit are consumed frequently and has an association with a lower cancer risk, studies have shown that they are protective against the head and neck, oesophageal and stomach cancer.^[21] In several studies it has been suggested that cruciferous vegetables help to regulate the enzymes that defend cancer, may help to stop cancer cell growth.[21] Sulforaphane present in the cruciferous vegetable especially in Broccoli showed anticancer properties. In a study it has been found that intake of cruciferous vegetables, measured by urinary secretion of isothiocyanates, was inversely related to the risk of breast cancer.^[21] In another study a high intake of cruciferous vegetables (5 or more servings/week vs. less than two servings/ week) was estimated to show 33% lower risk.^[21] Three or more servings per week, compared to less than one serving of cruciferous vegetables per week resulted in a statistically significant 41% decrease in prostate cancer risk.[21] Experimental studies on Moringa oleifera showed that the leaf extract is significantly able to retard the growth of cancer cells.[8] The extract also had prominent hepatoprotective effect. The extract did not influence proliferation of any normal cells indicating its safety for human consumption and use in pharmaceuticals.

[20] Thus, because of the health benefits of Moringa leaves, they can be eaten fresh, cooked, or crushed, and they can be stored as dried powder for several months without loss of nutritional value.

3.1.3 Whole Grains:

Many foods are considered as key elements for cancer prevention, and phytochemicals in whole grains are especially said to be important for prevention of cancer.[22] Whole grains are the edible seed of the grass family plants, which are composed of embryo, endosperm, starch granules, as well as the outside bran (fibre). These are highly adaptable to the environment and thus can be cultivated in different climatic and geographic conditions. Wheat, rice, millet, rye, barley, sorghum, oats, and maize are the most fundamental and important source of food and energy around the world.[23] Grains are rich in carbohydrates, proteins, minerals, and vitamins.^[23] Whole grains are rich in phytochemicals such as phenolic acids, carotenoids, alkylresorcinols (ARs), phytosterols, lignans, anthocyanins, vitamin E member and polysaccharides.[23] The anti-cancerous properties of whole grains are related to the dietary fibre functions that are effective in small intestine and colon, and therefore its effect is intensively studied cancer.[23] the colorectal The on phytochemicals also play a role in the anticancer activity which is been still investigated. After the experimental investigation it has been seen that bioactive compounds of whole grains exert anti breast cancer activity through inhibiting proliferation, modulating immune system, and inhibiting metastasis of breast tumour cells.[24] Table 2 presents the commonly used grains and their action towards cancer prevention.

Table 2 Whole grains and their mechanism.

Sr.no.	Whole	Bioactive Phytochemicals	Mechanism
	Grain		
1	Wheat	Alkylresorcinols	Induction of apoptosis and cell cycle arrest in colon cancer cells via
			activation of p53 pathway.[24]
2	Rice Bran	δ-Tocotrienol and Ferulic acid	Induces DNA damage in cancer cells, enhances apoptosis, inhibit cell
			proliferation and induce cell cycle arrest in G1 phase of cancer cells.[25]
3	Barley	Anthocyanins, Flavones, Tannins,	Up-regulation of apoptosis through lowering of metabolic activity, inhibition
		α -carotene/ β -carotene	of proliferation, and cell cycle arrest in G1 phase.[23]
4	Sorghum	Anthocyanins, Flavones	G1 phase arrest and Breast cancer tumour suppression.[23]
5	Oats	Avenanthramide	Activation of apoptosis and caspases activity and cell cycle arrest in sub G1
			indicating DNA fragmentation in breast cancer cells.[23]
6	Black Rice	Anthocyanins	Inhibit DNA binding activity and nuclear translocation of AP-1.[23]

Table 2: Table 2 enlists the examples of whole grains and their mechanism for prevention of cancer

3.1.4 Herbs and Spices:

According to the U.S. Food and Drug Administration (FDA), spices refer as "aromatic vegetable substance".[26] The increased research on spice is not only for their culinary properties but also for their potential health benefits. Though, the health benefits related to spice use may arise from their antioxidant properties, it has also biological effects that may arise from their ability to induce changes in several cellular processes, including those involving the metabolism, cell division, apoptosis, differentiation and immune modulatory.^[27] There are three types of biomarkers used to evaluate the effects of spices in cancer prevention and therapy - exposure, effect, susceptibility.[28] play Spices and а determining role to maintain the balance between pro and anti - cancer factors that regulates the risk and tumour behaviour.[29] It is seen that about 75% households in U.S. rely on the dietary approaches to reduce the risk of diseases, like cancer.^[29] More than 180 spice-derived compounds have been identified and explored for their health benefits, certain spices and herbs that have a positive effect on cancer prevention and therapy are discussed in table 3.

Sr.	Spices and	Role in cancer prevention
no	Herbs	
1	Cardamom	Ability to scavenge free radicals, inhibit chemical carcinogenesis, cardamom oil affects the enzymes associated with xenobiotic metabolism and have benefits as a deterrent to cancer, decrease azoxymethane-induced colon carcinogenesis by virtue of its anti-inflammatory, antiproliferative, and proapoptotic activities, enhance detoxifying enzyme (GST activity) and decrease lipid peroxidation.[28]
2	Cinnamon	In vitro Cinnamon extract potently inhibits various tumour cell growths and in vivo suppresses melanoma progression. Anti-cancer effect of cinnamon extract is mediated by apoptosis induction and blockade of NF-κB and AP1.[29]
3	Clove	Triterpenoid oleanolic acid (OA) most actively present in clove inhibits tumour Growth and Promotes Cell Cycle Arrest and Apoptosis.[30]
4	Coriander Seeds	Coriander exhibits anticancer activity by affecting antioxidant enzymes leading to H_2O_2 accumulation, cell cycle arrest at the G2/M phase and apoptotic cell death by the death receptor and mitochondrial apoptotic pathways.[31]
5	Cumin Seeds	Thymoquinone (TQ) present in cumin has antioxidant, antimicrobial, anti-inflammatory, and chemo preventive properties.[32] It ameliorates B(a)P-induced carcinogenesis in the stomach.[32] TQ suppresses tumour cell proliferation, including colorectal carcinoma, breast adenocarcinoma, osteosarcoma, ovarian carcinoma, myeloblastic leukaemia, and pancreatic carcinoma.[32]
6	Garlic	Garlic's characteristics arise from sulfur, which constitutes almost 1% of its dry weight, in which the primary sulfur- containing constituents are γ -glutamyl-S-alk(en)yl-L-cysteines and S-alk(en)yl-L-cysteine sulfoxides. Alliin (S-allyl cysteine sulfoxide) is the largest contributor in garlic. Preclinical models showed lower incidence of breast, colon, skin, uterine, oesophagus, and lung cancers.[33] The suppression of nitrosamine formation continues to surface as one of the most likely mechanisms by which garlic retards cancer.[33]
7	Ginger	Plays a major role in prevention of gastrointestinal cancer by induction of apoptosis through activation of caspase 3.[34] Plays a role as antiproliferative agent and augments the chemotherapeutic effect.[34] In cancer patients it helps to decrease the gastric dysrhythmia and reduces the delayed nausea of chemotherapy, decreases the incidence and multiplicity of adenomas in colorectal cancer and helps to increase the lymphocyte count in colorectal cancer patients.[34]
8	Curcumin	Induces apoptosis in many types of cancer cells, both intrinsic and extrinsic apoptotic pathways are activated.[35] Intrinsic pathway leads to irreversible DNA damage, defective cell cycle, or loss of growth factors- can generate death signals and ultimately passes them to mitochondria.[35] Curcumin modulates the pathogenesis of cancer proliferating signals by inhibiting the nuclear factor-kB at multiple steps.[35]
9	Honey	Honey has shown positive effect on cell cycle arrest.[36] Administration of honey with aloe vera is one the best solution to decrease the expression of Ki-67 in tumour cells.[36] Honey therapy is suggested to lower tumour proliferation by arresting cell cycle of colon, glioma, and melanoma cancer cell line in G0/G1 phase. The MTT assays have confirmed the anti- proliferative effect of honey is a dose and time dependant manner.[36] For example: Honey isolated from tea tree helps to prevent inflammation in the oesophagus caused by radiation and chemotherapy used for cancer treatment.[36]

Table 3 List of spices and herbs showing role in cancer prevention.

Table 3: Table 3 explains positive effect of spices and herbs on cancer prevention and treatment.

3.1.5 Millets:

Table 4 depicts the relationship between millets and its anti-cancerous properties.

	Table 4 Millets and its anti-cancerous properties.				
Sr.no	Millets	Effect against Cancer			
1.	Pearl Millet	It has a high fibre content which makes the grain to move slower from the stomach to small intestine and controlling the hunger thus, playing an important role in obesity-related cancers (multiple myeloma, colorectal, uterine corpus, gallbladder, kidney, and pancreatic cancers).[37] Has anti- cancer properties and prevents the tumour formation due to the presence of phenolic compounds.[37]			
2.	Finger Millet	The two nutraceuticals- phytochemicals and antioxidants have an extensive anti- carcinogenic property by acting as terminators of free radical and singlet oxygen species.[38] Finger millets consist of variety of such compounds that may suppress excessive cellular oxidation providing protection against different cancers prevalent in human population.[38] Ferulic acid found as the major constituent of bound phenolic acids in finger millet has blocking effect on induced carcinogenesis tongue, colon, and breast cancer cells, implicating as a natural bioactive chemotherapeutic agent against cancer.[38]			
3.	Proso Millet	The consumption of Proso millet have elucidated its effect on cancer. ^[39] It has been reported that caffeic acid, ferulic acid and syringic acid present in Proso millet has an anti- proliferative activity against the human breast cancer cells. ^[39] It is required to investigate more on the phytochemicals present in the Proso millet that are responsible for the antiproliferative activity. ^[39] It is also rich in bioactive phytochemicals, including ferulic acid, chlorogenic acid, syringic acid, caffeic acid and p-coumaric, having potential benefits to human health. ^[39]			
4	Foxtail Millet	Experimental studies showed that intake of foxtail millet attenuated colonic inflammation and reduced the risk of colorectal cancer, further studies are still needed to discuss the chemo-protective effects of foxtail on the progression of cancer in animal models and clinical trials, and to identify the bioactive components in this grain. ^[40]			
5	Barnyard Millet	Vanillin from Barnyard Millet significantly induced the apoptotic cell death in human colon cancer cell line (HT-29) and human breast cancer cell line (MCF-7) through apoptotic signalling pathway, during apoptosis processes, extracted compounds leads to the increase in the release of cytochrome c and upregulating the expression level of Bax (central cell death regulator) and caspase-9 as concentration increases in a dose-dependent manner.[41] Thus, vanillin can be used as an effective chemotherapeutic agent.[41]			
6	Little Millet	Niacin (vitamin B3) present in little millet can help lower cholesterol. It also helps in the prevention of breast cancer and reduces the risk of gastrointestinal conditions like gastric ulcers or colon cancer. [42]			
7	Kodo Millet	Antioxidants found in kodo millets, in addition to their beneficial impact on neutralizing free radicals, which can cause cancer, they can also clean up other toxins from the body, such as those in the kidney and liver.[43]			

Table 4: Table 4 review the role of millets in diet for prevention of cancer.

3.2 Fatty Fish (Omega-3 Fatty acids):

The recent have pointed out that the Omega-3 fatty acids, contained in oily fish such as salmon and trout, selectively inhibits the growth and induces cell death in early and late-stage oral and skin cancer.[44] Squamous cell carcinoma is one of the major forms of skin cancer, the cells also occur in the lining of digestive tract, lungs, and other areas of the body.[44] In vitro tests showed that omega-3 fatty acids present in salmon or trout induced cell death in malignant and pre- malignant cells when prescribed at doses that did not affect the normal cells Omega-3 fatty acids cannot be synthesized by humans on their own thus, it must be acquired in the diet through some medium.[45]

Cancer patients undergo complications during and after the treatment which include anorexia-cachexia syndrome, pain. depression, and paraneoplastic syndromes.[44] The beneficial effects of omega-3 PUFA consumption are likely related to its anti-inflammatory and proresolution effects, mainly due to the inhibition factor of nuclear factor kappa B (NF-kB) and the production of proresolution mediators, such as resolvins, protectins, and maresins.[45]

One of the most common complications related cancer to is cancer pain, approximately 90% of the patients suffer from it but unfortunately up to 50% of the patients are poorly treated.^[44] The pain occurs due to the tumour growth itself, development, metastasis or treatmentrelated adverse effects. such as chemotherapy-induced neurotoxicity.[44] In cancer survivors it is also important to note the pain as this condition can indicate a recurrence of tumour.[44]

Omega-3 FAs can be considered as pharmaconutrients, acting as receptor agonists, modulating molecular pathways, reducing the inflammatory response, increasing the chemotherapy efficacy, and consequently improving the overall survival of cancer patients.[44] EPA and DHA supplementation are helpful in the nutritional therapy of cancer patients and promotes beneficial effects during cancer treatment due to a membrane modulation. It plays an important role in [44] inflammation mechanism in the cancer patients.^[44] Omega-3 fatty acids present in fishes is rich in proteins and have low levels of carbohydrate thus not leading to obesity after its consumption.^[44] An important source of omega- 3 fatty acids are fish and oil seeds, particularly flax and Niger.^[44] Its daily intake recommended a minimum of 250- 500 mg combined EPA and DHA each day for healthy adult.

3.3 Probiotics:

There is a lot of evidence that the use of probiotics can play an important role in cancer prevention and support anti-cancer therapies. Probiotics refers live to microorganisms which, when administered in adequate amounts, confer a health benefit on the host. [46] The sources of probiotics in the human diet are cabbage, cucumbers, and fermented milk products (e.g., yogurt, kefir). The use of probiotics has a beneficial effect on the human gut microbiome.[46] The main advantage of probiotic is the effect on the development of the microbiota inhabiting the organism in the way ensuring proper balance between the bacteria that are necessary for a normal function of the organism and pathogens.^[46] The beneficial of probiotics lead to functions the restoration (in case of disturbance) and maintenance of intestinal homeostasis.[46] Cancer suppression and treatment of carcinogenic activity by probiotics are thus based on: (1) modification of the intestinal composition, microbiota (2)metabolic activity of the intestinal microbiota, (3) production compounds with of anticarcinogenic activity, such as shortchain fatty acids and conjugated linoleic acid, (4) inhibition of cell proliferation and induction apoptosis in cancer cells, (5) influence on other mutagenic and

carcinogenic factors, (6) binding and degradation of carcinogenic compounds present in the intestinal lumen, (7)immunomodulation and (8) improvement of the intestinal barrier.^[46] Probiotics play an important role by modulating the cellular proliferation and apoptosis as then the cancer cells would be eliminated less aggressively, and apoptosis brings no damage to the neighbour cells and does not cause inflammation.^[46] The apoptosis signalling pathways can be activated by probiotic bacteria (e.g., lactic acid bacteria; LAB) through pathways like mitochondriadependent (intrinsic) and a death receptormitochondria-independent dependent. (extrinsic) pathway.[46]

4. CONCLUSION

The new approach towards the nutrient synergy exemplifies the need for a better direction in taking advantage of multiple health benefits of food components in human health. Current research explains the red and processed meat, about, processed and canned foods that releases Nnitroso compounds., heme, polycyclic aromatic hydrocarbons and heterocyclic amines which are key mediators of DNA damage leading to triggering of oncogenes or inactivation of tumour suppressor genes. Indulgence with agents such as tobacco and alcohol are also contributing factors to DNA damage. In contrast, the foods such as cranberry, red grapes, strawberry, passion fruit, cruciferous vegetables, derivatives of whole grains, millets, spices, fish oil and probiotics contains the range of phytonutrients that inhibit the tumour growth, arrest the proliferation of cancer cells in G1 phase of cell cycle, induces apoptosis in various types of cancer cells and prevent metastasis. Thus, natural dietbased approaches are of great advantage in being non-oxidative, and protective to DNA damage with added value to serve as alleviator to the toxic effects of chemo and radiation therapies in prevention of cancer.

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Declaration by Authors

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