

# An Insight of Pulses: From Food to Cancer Treatment

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## Abstract

Cancer incidence is increasing due to the inclination of people towards western diet which consists of high fat, animal protein and refined carbohydrate content. Though, diet itself does not act as carcinogen but, it provokes the action of the former. Pulses form a significant component in the traditional healthy diets of many regions throughout the world due to its high nutritional value as well as its therapeutic effect on humans which mark them as nutraceuticals. The low fat, rich protein, dietary fiber, and a variety of micronutrients and phytochemicals have fueled speculation that, if consumed in sufficient quantities, they help to reduce tumor risk. Dietary fiber, resistant starch, phenolic compounds, phytosterols, oligosaccharides, etc. are the phytoconstituents present in pulses which contribute to the anticancer nature of pulses. The review pays a considerable attention on the potential role of pulses, highlighting the phytoconstituents responsible for preventing and treating cancer. However, the mechanisms of action behind them are unconvincing as pulses are used conventionally. There is a need to ascertain its quantitative contribution in reducing cancer risk as well as to utilize its cancer preventing constituents while developing food derived medicines.

**Keywords:** Leguminosae; Legumes; Proteins; Carbohydrates; Fats; Phytoconstituents; Diet

## Introduction

Cancer is a deadly disease spreading in both, developed as well as developing countries. This complex genetic disease can be caused by exposure to cancer-causing agents present in food, water, air, chemicals and sunlight. Epidemiology suggests a cancer-diet relationship where consumption of some dietary items increases the frequency of cancer. Many food materials increase the risk of cancer as more mortality has been reported in the places where people consumption of total fat, animal proteins and carbohydrates is very high [1-3]. The resistance of mammalian tumor cells towards conventional anticancer therapies, the high treatment cost, and the severe side effects associated with them, has reduced their clinical efficacy. Though, the science has significantly progressed in cancer therapeutics, discovery/ development of an efficient anticancer therapy with minimal side effects is the need of the hour. The phytoconstituents, either in the form of extracts, fractions or pure components, suggests lucrative results as compared to current cancer therapy [2,4]. The present review highlights the role of pulses in prevention and treatment of cancer. It also focuses on the phytoconstituents present in pulses imparting anticancer activity. The review has also described the effect of food/ diet on emergence of risk of cancer.

## Relationship between cancer and diet

The relationship between diet and cancer depends upon the type of diet consumed by a person. Though, the food items do not act as direct carcinogens, but, they promote the action of a carcinogen [2]. Epidemiology has also reported the effect of food and nutrition on cancer [5]. Carbohydrates, proteins and fats contribute maximum in releasing energy to the body. This excessive intake of energy individually, or in combination, increases the risk of cancer [6]. Figure 1 represents the effect of diet on human health.

**High fat:** Besides being a source of estrogen and oxidants, fat promotes many types of cancer such as breast and colon cancer, whereas, bears a less consistent correlation with cancer of ovaries, endometrium, testes, kidney and prostate. It has an insignificant, rather negative association with cancers of stomach, and liver [2,6-13]. A 10% hike in fat content increases the chance of recurrence of breast cancer by 4-8 times [14]. The effect of high saturated fat intake found in animal products; vegetable processed fat (mostly containing trans

double bonds, n-6 PUFAs such as linoleic acid) appear to enhance the promotional phase of carcinogenesis in preclinical models for breast and prostate cancers. It has been hypothesized by modulating sex hormone levels. These processed fats also increase risk of colon cancer in humans as it stimulates mutagenic secondary bile acid secretion [15-21]. Colorectal cancers also bear a strong association with such a high fat diet [22]. The fatty acids present in marine food sources reduce the risk of breast and prostate cancer. However, the literature contains an insufficient and unreliable data for the same [23,24]. Studies also suggest that many other types of fats, such as n-3 fatty acids, n-3 PUFAs (a-linolenic acid, eicosapentanoic acid, and docosahexanoic acid), are also inversely related to cancer risks [15,17,25]. A specific monounsaturated fatty acid (MUFA), oleic acid found in olive oil, possess the potential of inhibiting carcinogenesis, especially breast cancer [26,27].

**High protein:** Proteins found in animals' meat, especially processed and red meat, beef, is closely as well as positively correlated with various forms of cancer [2,22]. Animal proteins have a positive association with breast, ovary, prostate, colon and large bowel cancers [8,9,13,28,29]. The mechanism might relate to effect of cooking (frying and boiling) on dietary haem found in red meat at high temperature or the effect of meat on hormone metabolism [6,30-32]. Many scientists have established a positive effect of high protein intake on colorectal cancer [22,33-35]. It has a negative association with gastric cancer [36]. Contrary to above findings, many epidemiologic studies suggest that a high protein diet does not stimulate cancer risk [25].

**Refined carbohydrates:** Dietary carbohydrates include starches (e.g., bread, pasta, other grains), non-starch polysaccharides (the major component of dietary fiber), and sugars [6,37]. Firstly, sugars

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remarkably lower the immune system's ability to work properly which may lead to abnormal response of immune system towards the carcinogens [14]. Secondly, breaking of excess of carbohydrates into energy needs excess of insulin which may trigger breast cancer just as estrogen does. Elevated levels of insulin and insulin like growth factors drastically increase the risk of colorectal, prostate and premenopausal breast cancer [38-43]. Still, some studies of colon and breast cancer did not find an association between diets high in glycemic load/ sugar and cancer [44,45]. There are many other dietary components imparting minor or misleading effect on cancer such as calcium, dairy products etc. [46].

**Pulses:** Though animal proteins are considered as the richest source of proteins, they are accompanied with its high cost due to which, they are inaccessible to the poorer section of the population. Legumes are considered as poor man's meat which is a good and cheap source of slow release carbohydrates, rich proteins, minerals and vitamins. Legumes are classified into three categories, namely grains, peas, and beans. Whole, dehusked and split grains (commonly known as dhals) are extensively used for human consumption [47-49]. The germination of the legumes increases their vitamin C level. However, in some, riboflavin as well as niacin content is also increased [48]. The activity of many enzymes such as amylase, protease, phytase and lipase also increase during germination [50] Heat treatment increases the palatability of food and bioavailability of nutrients. Pulses play an important role not only in human nutrition, but also impart beneficial physiological effects by controlling and preventing various metabolic diseases [49]. Nutraceuticals or functional foods are the new generation of food products which are developed on the evidence of the positive impact of some food components on human health, mostly with the addition of bioactive components that display a therapeutic effect [51].

**Role of pulses in cancer:** It has been studied that the people majorly dependent on plant foods tend to have a lower rate of cancer [52]. Pulses, an important constituent of plant food, are rich in many constituents which can prove to be responsible for preventing as well as suppressing cancer. Figure 2 lists the phytoconstituents present in pulses which contribute to the anticancer attribute of pulses.

**Dietary fibers:** Dietary fibers (DF) are generally defined as the macromolecules present in the diet that can be water insoluble (cellulose, lignin, some hemicelluloses) or water soluble (pectins, gums, mucilages and some hemicellulosic fractions), resistant starch, other polysaccharides and, a non-carbohydrate polymer of phenyl propane residues. They resist digestion by human endogenous enzymes. They exhibit a significant role in prevention of colon, colorectal and breast cancer [53-55]. Dietary fibers protect the humans against colon cancer risk through various proposed mechanisms. Increasing faecal bulk (diluting carcinogens); increasing transit time through the colon (reducing interactions of carcinogens with mucosal cells); direct binding of carcinogens; modifying the enzyme activities of intestinal bacterial flora (decreasing concentrations of secondary bile acids); and producing short-chain fatty acids (SCFAs) by fermentation may inhibit carcinogenesis through effects on colonic pH [54,56,57]. Evidence suggests that fat and fiber interact to influence apoptosis. Dietary pectin, a fiber that produces high amounts of butyrate during fermentation, enhances the up-regulation of apoptosis by in experimentally-induced colon cancer [58]. The water soluble dietary fibers protect against colon cancer through microbial fermentation in the large intestine [49].

**Resistant starches:** Resistant starch (RS) is the fraction of starch which is not hydrolyzed in the small intestine but later, fermented by the colonic microflora [59]. *In-vitro* studies with human faeces prove

that fermentation of RS yields relatively high amounts of butyrate which are the supposed markers of colonic health of humans [60]. It has also been suggested that butyrate induces apoptosis along with stimulation of histone acetylation. It also down regulates bcl-2, which is an oncogene that acts by blocking apoptotic cell death [49,57,58,61-64].

**Phytic acid:** Phytic acid is a potential active ingredient found in inositol hexaphosphate (IP6) which is a naturally occurring substance. It is present in most of the legumes, especially high fiber diets [65-71]. It has been revealed that phytic acid inhibits neoplastic growth in multiple types of cancer including breast, colon, liver, prostate, rhabdomyosarcoma and skin. It inhibited the development and progression of tumor cells by significantly reducing tumor number, incidence and multiplicity [65,69,72-77]. An increase in natural killer cell activity, alteration in signal transduction, stimulation of genes towards greater cell differentiation and antioxidant activity are the hypothesized mechanisms acting behind the anticancer activity of phytic acid [78-81].

**Saponins:** Presence of saponins has been reported in more than 100 families of plants [82]. The Leguminosae family predominantly consists of triterpene saponins [83]. The main dietary sources of saponins in legumes are soybeans, chickpeas, mungbeans, peanuts, broad beans, kidney beans, lentils, etc. [84]. A number of pulses containing saponins have reported to exhibit anticancer activity [85-88]. Soybean saponins are renowned anticarcinogens which is evident from many cell culture studies and few animal studies [86]. The effect of soybean saponins on colon cancer has been studied by Gurfinkel et al. [89].

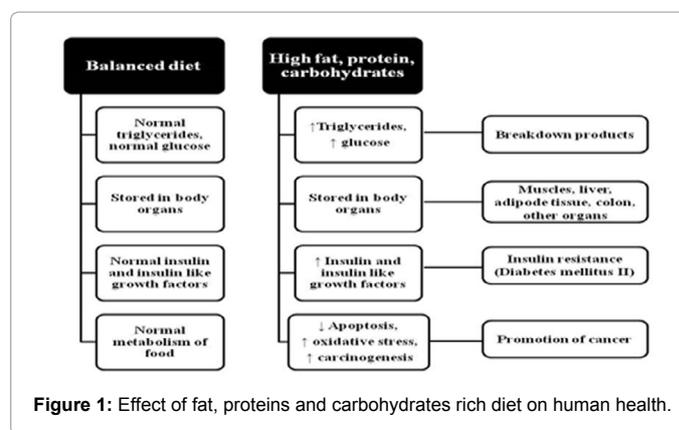


Figure 1: Effect of fat, proteins and carbohydrates rich diet on human health.

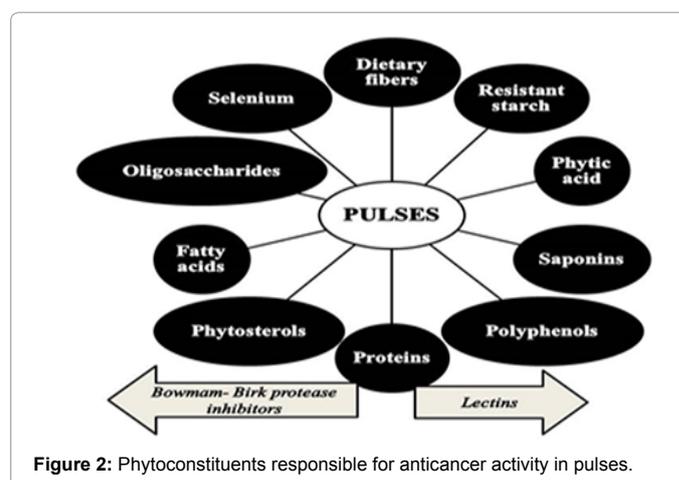


Figure 2: Phytoconstituents responsible for anticancer activity in pulses.

**Polyphenols:** Phenolic compounds serve many diverse functions in a plant such as coloring the leaves and fruits, attracting or repelling insects and protecting plants from herbivores. Fruits, vegetables, leaves, nuts, seeds, flowers, and barks contain a high amount of phenolic compounds [90,91]. Many phytochemicals which include phenolic compounds such as flavonoids, nitrogenous compounds such as chlorophyll derivatives, as well as tocopherols, carotenoids, and ascorbic acid exhibit antioxidant activity. Epidemiological studies have found a positive correlation between ingestion of polyphenolic compounds and improved health. Plant phenolic compounds and fruit extracts exhibit significant antioxidant activity which also inhibits mutagenesis and carcinogenesis [92-98]. Authors also report polyphenols exhibiting antiproliferative and cytotoxic potentials in several tumor cell lines [99,100]. Phenolic acids are a type of polyphenols which are distributed in plants as hydroxycinnamic acid, chlorogenic acid, etc. Caffeic acid phenethyl ester acts as anticancer compound by inhibiting metastasis. Para- coumaric acid also possess anticancer activity. Ferulic acid and caffeic acid have shown to act as both, carcinogens as well as anticarcinogens. They act by inhibiting formation, activation and uptake of carcinogen. They also deactivate or detoxify the carcinogens, preventing the carcinogen binding to DNA, and enhancing DNA repair [101,102].

Catechins are a type of polyphenols which contribute to the bitterness and astringency of food. Epigallocatechin-3-gallate, epigallocatechin and galocatechin are reported to exhibit high anti-proliferative action against three cancer cell lines, i.e., MCF-7 breast cancer, HT-29 colon cancer and UACC-375 melanoma cancer [103].

Flavonols are polyphenolic secondary plant metabolites, the major representatives of which are quercetin, myricetin, kaempferol, and isorhamnetin. Quercetin acts as an anti-proliferative agent by inhibiting cell proliferation, cell growth, and cessation of cell cycle of colon, breast, gastric, oral, prostate and ovarian cancer cells [104-110]. Studies on kaempferol are few but are contradictory as their proliferative/ anti-proliferative activity is based on its concentration. Its anticancer effect was found on human lungs and breast cancer cell lines, whereas, the proliferative effect was observed by Wang et al. [111-113]. The mechanism by which the flavonols act as anticancer compounds is the controlled cell growth, cell cycle, cell proliferation and increased apoptosis [101].

**Proteins:** During the development of legume seeds, a large amount of proteins accumulate and then, get stored in membrane-bound organelles, the storage vacuoles or protein bodies. They survive desiccation in seed maturation and undergo proteolysis at germination, thus providing free amino acids, as well as ammonia and carbon skeletons to the developing seedlings. These seed proteins are termed as storage proteins [114]. The legume seeds are among the richest food sources of proteins and amino acids for human and animal nutrition. They contain several minor proteins such as protease and amylase inhibitors, lectins, lipoxygenase, defense proteins and others. They contribute to the nutritional/functional quality of the seed or play a storage role by virtue of their amount in the seed. The legume storage proteins are relatively low in sulphur-containing amino acids, i.e., methionine, cysteine and tryptophan, but the amounts of another essential amino acid, i.e., lysine, are much greater than in cereal grains [56,115,116]. Among the legume proteins, two components, i.e., protease inhibitors and lectins, play an important role in exhibiting anticancer properties. Their irreversible action of inhibiting various digestive enzymes is only observed if the pulses are consumed in raw form. Once the legumes are cooked (heat denaturation), the anti-

nutritional compounds get inactivated and then, they play a positive nutritional role [117]. Protease inhibitors especially Bowman-Birk inhibitors, are closely related to prevention and blocking of certain tumour pathologies [118-122]. Lectins are the other component of proteins which limit tumour growth by binding to cancer cell membranes or their receptors, followed by causing cytotoxicity, apoptosis, and inhibition of tumor growth [123,124].

**Bowman-Birk protease inhibitors (BBI):** Though, the classical representative of BBI is soybean but, it is being obtained, gradually identified and characterized from other monocotyledonous and dicotyledonous seeds of Leguminous plants such as rice bean (*Vigna umbellata* T), red kidney bean (*Phaseolus vulgaris*), brazilian pink bean (*Phaseolus vulgaris*), lima bean (*Phaseolus lunatus*), adzuki beans (*Phaseolus angularis*), chickpea (*Cicer arietinum*), pea (*Pisum sativum*), lentil (*Lens culinaris*), and pigeon pea (*Cajanus cajan*, syn. *Cajanus indicus*) [125-140]. It has been found as an effective chemopreventive agent against prostate cancer in animal models by blocking the generation of reactive oxygen species in prostate cancer cells [141]. It is reported that it can also cure breast cancer. As BBI is cost-prohibitive for clinical studies, a crude BBI concentrate (BBIC) was prepared which contained BBI, soybean cystatin, soybean trypsin inhibitor, isoflavones, saponins [142,143]. *In vitro* studies using BBI have demonstrated that BBI alone is an anticarcinogen that is effective at nanomolar concentrations and has irreversible effects on cancer cells [120,121,144,145]. However, it is difficult to associate all the chemopreventive properties of BBIC to BBI alone because saponins and isoflavones have been reported as anticarcinogens and antiangiogenic [86,144,146]. BBI bears a unique property of reversing the initiated state of cells after initiation of cancer [121,147]. It was also found to shrink pre-cancerous lesions in the mouth that lead to oral cancer called leukoplakia [148,149].

**Lectins:** Lectins are a very important group of biologically active glycoproteins found in vegetative tissues, leaves, stems, bark, bulbs, tubers, corms, rhizomes, phloem, fruits, and flower tissues [150,151]. They are considered to be toxic as well as anti nutritional in nature. But, many are non toxic such as those from lentils (*Lens culinaris* agglutinin), peas (*Pisum sativum* agglutinin), faba beans (*Vicia faba* agglutinin), soybean (Soybean agglutinin) and other common foods. They are highly used for diagnostic as well as therapeutic purposes in cancer research. They act by stimulating the immune system, binding to tumoral cell membranes, reducing cell proliferation and inducing apoptosis. A strong correlation between lectin-binding patterns and anticancer activity has been reported where the effect of lectins on normal and cancer cells was also studied *in vitro*. Lectins have different carbohydrate-binding specificities, the effects of which have been studied on human hepatoma (H3B), human choriocarcinoma, mouse melanoma, and rat osteosarcoma cell lines [152,153].

**Phytosterols:** Phytosterols are the sterols present in plants and they are the unsaturated cyclopentanophenanthrene ring system composed of 28 or 29 carbon atoms with a side chain at carbon C17. Plants generally contain  $\beta$ -sitosterol (24 $\alpha$ -ethylcholesterol), campesterol (24 $\alpha$ -methylcholesterol) and stigmasterol ( $\Delta$ 22-24 $\alpha$ -ethylcholesterol) and their unsaturated equivalents, i.e., stanols [154-157]. Phytosterols are reported to act as anticancer agents against esophageal, colon, prostate, stomach and breast cancer by inducing apoptosis of the respective cultured cancer cells [158-164]. But, phytosterols are not associated with a reduced risk of rectal cancers [165-167].

**Oligosaccharides:** Oligosaccharides are the polysaccharides

which bear a low (2-20) degree of polymerization [168]. They act as soluble dietary fibers in human gut as they have the ability to alter the human faecal flora. They promote the health of colon by promoting the growth of bifidobacteria. It has been suggested that it improves, rather increases longevity, and decreases colon cancer risk [169-174].

**Fatty acids:** Pulses are generally low in fat content but they contain many fatty acids which are favorable in reducing cancer risk such as oleic, linoleic acids, etc. [165,167,175].

**Selenium:** Selenium is an important constituent of pulses which are potent in killing invading pathogenic bacteria and fungi, hence increasing the cell mediated immunity of a person. It plays a putative role in removing viruses and destruction of neoplastic cells [176]. Many forms of selenium act as anticancer agents due to their defensive effect at early as well as later stages of carcinogenesis and its progression. The mechanism of action might involve their ability to inhibit tumor cell migration and stimulation of cell apoptosis [177].

### Future Research Strategies

Pulses contribute not only as an important part of the healthy and balanced diets, but they also reduce the risk of cancer risk at several sites due to the presence of several bioactive micronutrients and phytochemicals. Still, in developed countries, they are not used much due to the inclination towards excessive energy diet consisting of animal proteins, high fat and refined carbohydrates. As the nutrient profile and therapeutic contribution of pulses is known, an attention should be paid to encourage the people to consume more pulses. As the quantitative contribution of pulses to treat cancer is yet to be worked on, the well-designed animal studies should be carried on to determine the former. The pulses should be used as nutraceuticals where the bioactive constituents are isolated and formulated into a suitable formulation for treatment of cancer.

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