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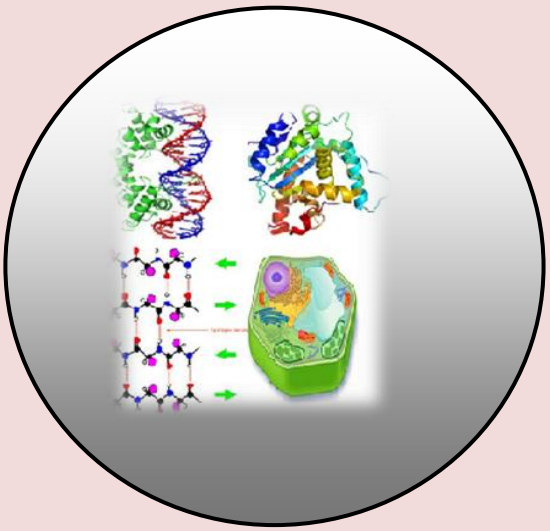
ISSN 2319-3077 Online/Electronic
ISSN 0970-4973 Print

UGC Approved Journal No. 62923
MCI Validated Journal
Index Copernicus International Value
IC Value of Journal 82.43 Poland, Europe (2016)
Journal Impact Factor: 4.275
Global Impact factor of Journal: 0.876
Scientific Journals Impact Factor: 3.285
InfoBase Impact Factor: 3.66

J. Biol. Chem. Research
Volume 36 (1) 2019 Pages No. 74-85



Journal of Biological and Chemical Research

An International Peer Reviewed / Referred Journal of Life Sciences and Chemistry

Indexed, Abstracted and Cited in various International and National Scientific Databases

Published by Society for Advancement of Sciences®

J. Biol. Chem. Research. Vol. 36, No. 1: 74-85, 2019
(An International Peer Reviewed / Refereed Journal of Life Sciences and Chemistry)
Ms 36/01/42/2019

ISSN 2319-3077 (Online/Electronic)
ISSN 0970-4973 (Print)

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RESEARCH PAPER

Received: 01/11/2018 **Revised: 16/01/2019** **Accepted: 18/01/2019**

Bioactive Constituents in Pulses- A Healthy way to Combat Cancer

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ABSTRACT

According to the International Agency for Research on Cancer (IARC) the incidence of cancer is increasing due to the tendency of individuals towards processed foodwhich consists of high fat, animal protein and refined carbohydrate content. The consumption of nutritional foods that are rich in beneficial bioactive constituents(polyphenols, phytosterols, resistant starch, saponins and dietary fibre) have a significant effect on reducing the risk of cancer. Pulses form a main 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. They not only provide a significant amount of proteins, carbohydrates and micronutrients but are also rich in bioactive constituents that are beneficial for managing and preventing diabetes, heart problems, obesity and certain types of cancers. Keeping in view the bioactive constituents present in pulses and therapeutic use, demand has increased for its human consumption either to extract a functional compound (e.g., starch protein or fiber) to incorporate this into cereal-based products or to extract phytocompounds which are bioactive and can be used as nutraceutical products. The present review pays a considerable attention on the potential role of pulses, highlighting the phytoconstituents responsible for preventing and treating cancer. There is a need to ascertain the quantitative contribution of pulses in reducing cancer risk as well as to utilize its cancer- preventing constituents while developing food derived medicines.
Keywords: Pulses, Bioactive compounds, Nutraceutical and Chemoprevention.

INTRODUCTION

Pulses are members of the *Leguminosae* family that are harvested exclusively for the dry seeds. They are rich in macronutrients such as proteins (5-10%), carbohydrates (50-65%), fibre (4-7%) and are low in calories and fat(Marinangeli et al., 2011). General health benefits of pulses have been associated with these macronutrients. There are also sufficient evidences that suggest some non-nutritional compounds present in them also play a significant role in the maintenance of human health(Mahadevappa and Kwok, 2017). These non-nutritional components includeenzyme inhibitors, phytic acid, lectins, phytosterols, phenolic compounds and saponins which make pulses suitable for application in wide range of food products(Tiwari et al., 2011). The food and Agriculture Organization of United Nations (FAO) declared 2016 as International Year of Pulses in order to highlight the important nutritional properties and the low environmental impact of pulse production

worldwide (FAO, 2016). A large range of species of grain legumes are cultivated and consumed throughout the world. Experimental, epidemiological and clinical studies show correlations between the consumption of food legumes and decreasing incidence of cancers(Mathers, 2002;Tiwari et al., 2013).The components particularly carotenoids, polyphenols, phytosterols and dietary fibers, have been shown to reduce the risk of major chronic diseases of humans such as cancer, cardiovascular diseases, and Parkinson's disease(Mahadevappa and Kwok, 2017). Such bioactives are therefore good candidates for ingredients of nutraceutical.This review highlights the important contribution of pulses not only in healthy and balanced diet, but also their role in reducing the risk of cancer due to the presence of several bioactive micronutrients.

Pulse Sector in India

India's economy has been dominated by agriculture and is the largest producer and consumer of pulses in the world(Singh et al.,2015). The total consumption of various pulses and pulse products in India is about 21-22 million tonnes. India's annual pulse production is about 18.45 million covering an area of about 23.47 million hectare. Among the pulses, chickpea contributed 48%, Pigeonpea 17%, blackgram, 10%, greengram 7% and other pulses 18% towards total pulses production (Patrons, 2017). Some of the commonly consumed pulses in India are listed in Figure 1.

Pulses as a source of anticancer compounds

A broad diversity of compounds (polyphenols, enzyme inhibitors, dietary fibre, resistant starch and saponins) of plant origin have been reported to exhibit anticancer activity through various molecular pathways (Table 1). Development of new small molecules is based on the discovery of bioactive secondary plant metabolites and new phytochemical drugs that target tumor angiogenesis and induce apoptosis in cancer cells(Upadhyay and Dixit, 2015). Various cancer preventive mechanisms have been identified as affected by dietary components, including prevention of oxidation, detoxification of xenobiotics, induction of apoptosis, stimulating effects on immune system function, anti-inflammatory properties and their effects on the cellular signaling system(Shen et al.,2007). Among these are effects on nuclear factors, such as NF-κB or activator protein 1 (AP-1), which play central roles in cellular signaling cascades, regulating DNA transcription, gene expression in response to different stimuli, cell proliferation and survival (Figure 2).

Polyphenols

Polyphenols that include flavonoids, phenolic acids, lignans and stilbenes comprise a diverse group of secondary metabolites abundant in plants, where they play key roles in regulating growth, metabolism, protecting against UV radiation and cancer (Scalbert et al.,2005). Flavonoids and phenolic acids are the dominant phenolic compounds present in lentils, black gram, peas and common beans (Xu and Chang, 2007). Ombra and co-workers have reported that the extracts of *Phaseolus vulgaris* showed significant antioxidant activity, and the in vitro antiproliferative activity against the human epithelial colorectal adenocarcinoma (Caco-2) cells, human breast cancer cells (MCF-7) and lung cancer (A549) cell line (Ombra et al., 2016).

Recent studies have revealed the presence of important polyphenolic compounds from the pulses through high performanceliquid chromatography-diode array detection (HPLC-DAD) analysis. These include Gallic acid, Delphinidin 3,5-diglucoside, Cyanidin 3-glucoside, Chlorogenic acid, (+)-Catechin, (-)-Epicatechin, Caffeic acid, Syringic acid, Rutin, p-Coumaric acid, Kaempferol 3-glucoside, Ferulic acid, Resveratrol and Quercetin(Giusti et al., 2017).Their action can be ascribed not only to their ability to act as antioxidants but also to their ability to interact with basic cellular mechanisms. Such interactions comprise of interference with membrane and intracellular receptors, modulation of signaling cascades, interaction with the enzymes concerned with the tumor promotion and metastasis, interaction with oncogenes and oncoproteins, and especially direct or indirect interactions with nucleic acids and nucleoproteins. Particular interest in these naturally occurring plant components have trigerred search for new chemopreventive agents that are more efficacious and less toxic than conventional therapies.

Protease Inhibitors

Plant protease inhibitors (PI) are multifunctional proteins which protect plants against diseases, insects, pests, and herbivores. In the past, PIs were considered primarily as protein-degrading enzymes. However, this view has significantly changed and PIs are now treated as very important signaling molecules in many biological activities such as inflammation, apoptosis, blood clotting and hormone processing (Cruz-Huerta et al., 2015). The European Cancer Proteases Consortium (EUCPC) has proposed multi- disciplinary research considering extracellular proteases as an attractive target for intervention against cancer(Pandey et al., 2007). Interestingly, many plant-based PIs are also found to be effective against cardiovascular diseases, osteoporosis, inflammatory diseases and neurological disorders(Wang et al., 2006).

Among all types of PIs, Bowman-Birk inhibitors (BBI) have been studied to a great extent in the treatment of many diseases, especially in the field of cancer prevention. So far, crops such as beans, potatoes, barley, squash, millet, wheat, buckwheat, groundnut, chickpea, pigeonpea, corn, and pineapple have been identified as good sources of PIs(Correa, 1981).The legume seeds are among the richest food sources of proteins and amino acids for human and animal nutrition(De Mejia and Dia, 2010).Among the seed legumes, the serine proteinase Bowman-Birk inhibitors (BBI) and Kunitz type inhibitors (KTI) have been studied extensively(Macedo et al., 2000). In common beans, lima beans, cowpeas, and lentils protease inhibitors have been characterized as members of the Bowman-Birk family (Godbole et al., 1994). Therefore, plant protease inhibitors regulating proteases have a very remarkable role to play in human health and disease management (Table 2). Extensive *in vitro* and *in vivo* studies and clinical trials have established the potentiality of plant protease inhibitors in inhibiting different stages of carcinogenesis including initiation, promotion and progression.

Numerous studies have shown that legumes can act as possible protective agents against several types of cancer such as breast, colon, and prostate (Table 3). BBI extracted from legumes have already received approval for human trials from the US Food and Drug Administration and have been demonstrated to play important roles in several biological processes related to the development of colorectal cancer, including inflammatory disorders, cell growth regulation/dysregulation and angiogenesis(Kennedy, 1998).

Lectins

Plant Lectins (Amaranthin, *Agaricusbisporus* agglutinin, Cyanovirin, Chitinase-related agglutinin, *Euonymus europaeus* agglutinin, *Galanthusnivalis* agglutinin (GNA), Hevein, Jacalins, Lysine motif, proteins with legume lectin domains, Nictaba, and Ricin-B families)(Damme et al., 2007) have the ability to induce apoptosis through different pathways, some being more effective than others in specific cell lines(Ya et al., 2015). This property being attributed due to over production of caspases or other proteins involved in the molecular pathway. Such pathways can lead to down-regulation or up-regulation of some genes involved in apoptotic suppression or induction, respectively. Certain miRNA act as inhibitors of ribosomal inactivating proteins (RIPs) and can be down-regulated through lectin activity thus allowing RIPs to function properly and inhibit neoplastic growth (Fu et al., 2012). Reports are available for Soybean lectin to have antiproliferative effect, apoptosis, and autophagy induction by oxidative stress and DNA damage and Inhibition of tumor growth under in vivo conditions.

Dietary fibre

American Association of Cereal ChemistsInternational (AACCI) have included dietary fibre as the edible part ofplants and analogous carbohydrates that resist the digestion and absorption processes in the human small intestine with partial or complete fermentation in the large one(Rebello et al., 2014). Pulses are good source of dietary fibre and contain both soluble (SDF) and insoluble (IDF) fibre, the latter being the major portion of pulse dietary fibres (Wang and Toews, 2011). Pulse SDF constitutes gums, pectins, fructans, inulins, and some hemicelluloses, whereas IDF included cellulose, some hemicelluloses, lignins, and arabinoxylan(Rebello et al., 2014). The interaction of fibres with other bioactive constituentse.g. polyphenol also influences the physiologicalproperties and health benefits of dietary fibres through the formation of hydrogen andhydrophobic linkages between polyphenols and cell wallcomponents(Duenas et al., 2016).

Several modes of actions however have been proposed for the dietary fibres to act as anticancer agents. First, dietary fiber (DF) have the property to resists digestion in the small intestine, this allows it to enter the large intestine where it is fermented to produce short chain fatty acids, which have anti-carcinogenic properties(Young et al., 2005). Second, the DF helps in fecal bulking and viscosity, there is less contact time between potential carcinogens and mucosal cells. Third, DF increases the binding between bile acids and carcinogens. Fourth, there is an enhancement in the level of antioxidants upon the increased intake of dietary. Fifth,the higher intake leads to increase in the amount of estrogen excreted in the feces due to an inhibition of estrogen absorption in the intestines (Adlercreutz et al., 1994). Increased consumption of fibres conferred additional benefits with Colo rectal cancer patients (Song et al., 2017).

Saponins

Among different bioactive component saponins have attracted a considerable interest of researchers due to itsanticancer property and significant importance in reducing the risk ofcancer(Shi et al., 2004).Saponins have the ability to knock out tumour cells from body(Leterme, 2002). The anticarcinogenic properties of saponinsinvolve mechanisms such as acid and neutral sterol metabolism,cytotoxicity of cancerous cells, immune modulatory effects andnormalization of carcinogen-induced cell proliferation(Long and Chen, 2014).

Saponins show cytotoxic and growthinhibitory effects on colon tumour cells in cultures probably byinteracting with the free sterols or cholesterol present in the cellmembrane and by changing its permeability (Rao and Sung, 1995),(Gurfinkel and Rao, 2003) The consumption of naturally occurring antimutagenic or anticarcinogeniccompounds through food has been suggested as aneffective way for cancer prevention. Berhow and co- workers examinedthe antimutagenic potential of saponins in mammalian cells andreported that these molecules may intercept or compete with thereactive molecules and suppress their potency or activity.

Antioxidant property of saponins is attributed to their free radical scavenging activity. It has been reported that DDMP-saponins can prevent the damage caused by the attack of free radicals (Yoshiki, Jin-Hyeong, & Okubo, 1994). Pulses such as chickpeas, beans, lentils, peas and lupin are the main sources of dietary saponins.Saponins are categorized into A, B & E group saponins according to their aglycone structures. Group B saponins were reported to bethe main saponin components in pulses(Shi et al., 2009).Numerous evidences suggest that legume saponins may possess anti-cancer activities in melanoma cell, cells (Chang et al., 2006),Colon Cancer(Gurfinkel and Rao, 2003) and cervical cells (Xiao et al., 2007).Table 3liststhe anticancer property of some of the dominant saponins.

Resistant Starch

Resistant Starch (RS) has received much attention for both its potential health benefits and functional properties**.** Starch, a storage carbohydrate, constitutes a major proportion (45–65 % of dry matter and 70–75% of total carbohydrates) of almost all pulses(Ratnayake and Jackson, 2008). Although it is the primary available carbohydrate in pulses, not all of it is digested and metabolized in the body. The digestibility of starch and thereby the resistant starch content are influenced by several factors that affect its accessibility to enzymes such as the structure of the starch granule and whether it is disrupted or intact. Resistant starch is an extremely broad and diverse range of materials and is divided in four categories (RS1–4) (Nugent, 2005). Category one (RS1) is starch physically protected from digestive enzymes in grains that haven't been fully milled. Category two (RS2) refers to starch in less stable, tightly packed crystalline granules that are partially resistant to hydrolysis. Category three (RS3) is starch (amylose) that has been retrograded into more highly stabile crystalline structures, and category four (RS4) refers to starch that has been modified using chemical reagents. RS3 is considered the most stable of the natural resistant starches to heat (over 100 °C) and further processing. Upon entering the colon, RS undergoes a high degree of anaerobic fermentation by local microbiota into a wide variety of products. These products include gases (hydrogen, methane, and carbon dioxide) and short-chain fatty acids (acetate, propionate, and butyrate). Pulse grains are high in RS and retain their functionality even after cooking (Rochfort and Panozzo, 2007). It significantly promotes large bowel health and preventing bowel inflammatory diseases and colorectal cancer (Topping et al., 2003).

This review suggested that the pulses are carriers of several bioactive constituents of potential biological importance which contribute suppression of cancer invasion.

(a)Split Bengal gram (b)Black gram (c)Chick pea (d)Kidney beans (e) Horse gram (f) Green gram (g) Lentil (h)Pigeon pea

Figure 1. Commonly consumed pulses in Indian region.

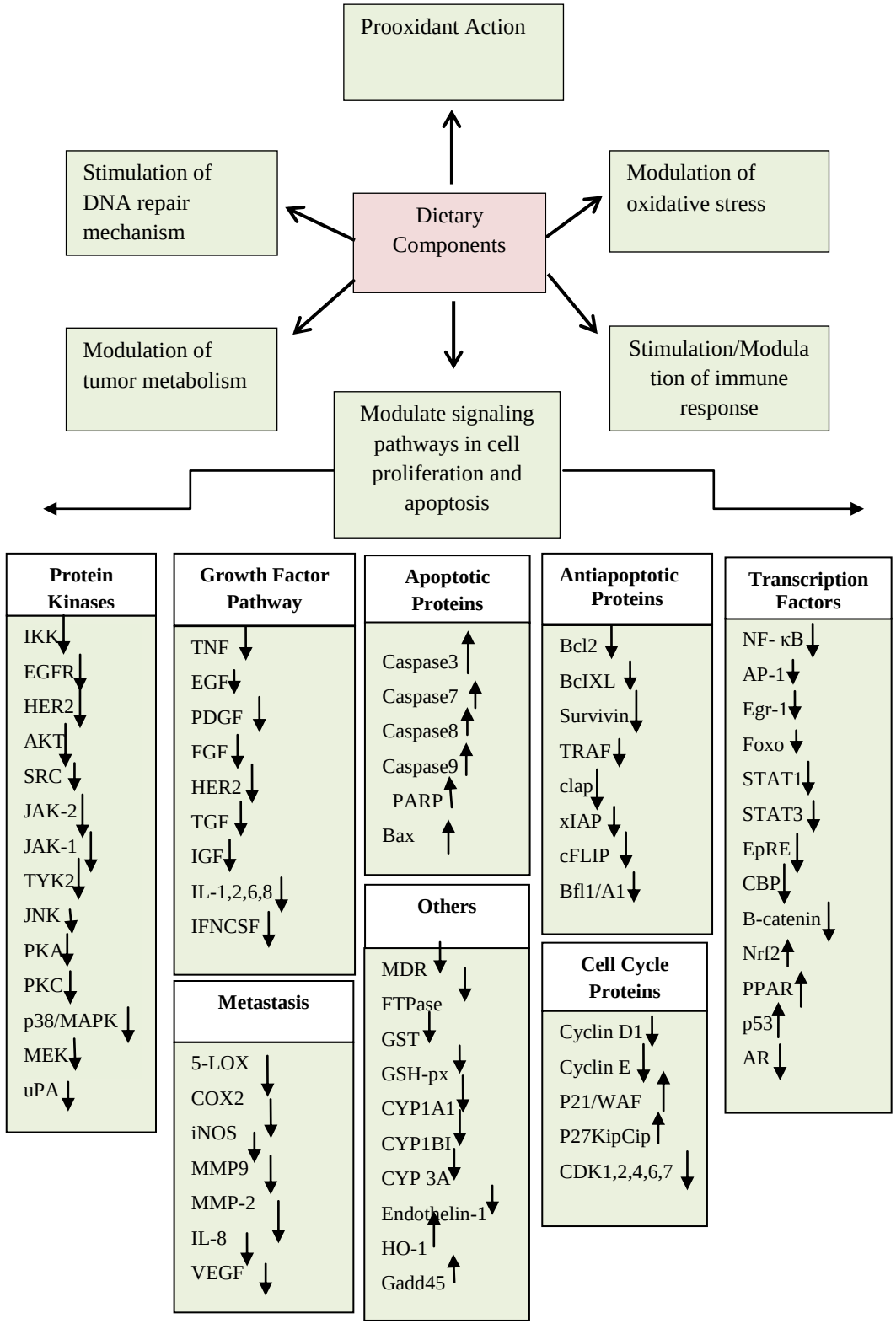

Figure 2. The role of dietary components in the modulation mechanisms in carcinogenesis.

Table 1. Anticancer properties of bioactive constituents present in pulses.

Pulses	Health Benefit	Bioactive Constituent	References
Pulses	Prevent colon, breast and prostate cancer	Resistant starch, Oligosaccharides, Isoflavones, Phytosterols	(Mathers, 2002) (Park et al., 2009)
Common Beans	Inhibition of proliferation of the human epithelial colorectal, breast cancer and lung cancer	Polyphenols, Polysaccharides, Lectins	(Chan et al., 2012; Feregrino-Pérez et al., 2008; Ombra et al., 2016)
Faba Beans	Anticancer and antioxidant properties Slows progression of colon cancer Antiproliferative activity towards liver cancer	Polyphenols, Polysaccharides, Lectins, Trypsin inhibitor (Viciafaba cv. Giza 843)	(Siah et al., 2012) (Jordinson, El-Hariry et al., 1999) (Fang et al., 2011)
Black gram	Protection against DNA and erythrocytes from oxidative damage and their cytotoxic effect on HeLa cells	Flavones	(Girish et al., 2016)
Horse gram	Horse gram seed germination maximally inhibited by vinblastine and the cancer palliative herbal drug HST-K drug.This enables the exploration of horse gram for safer remedies for cancer	Enzymes	(Athreya and Menon, 2016),
	Horse gram at sprouts stage prevented breast cancer	Isoflavones:genistein and diazein	(Sukanya and Gayathri, 2014)
Adzuki beans	Antiproliferative activity against digestive system, ovary and breast cancer	Phenolics, Phytic acid, Saponins	(Xu and Chang, 2012))
	Stimulation of dendritic cell maturation and induction of apoptosis in leukemia	Flavanoids, Saponins	(Nakaya et al., 2012)
Pigeon Pea	Cajanol possessed stronger cytotoxicity activity towards A549 cells	Isoflavones	(Zhao et al., 2013)
	Exerts an anticancer effect on breast cancer	Cajaninstilbene	(Fu et al., 2015)
Broad Bean, Mung Bean, Chickpea,Soybean	Antiproliferative effect, apoptosis, and autophagy induction	Isoflavones: genistein and diazein	(Berhow et al., 2000., Kerwin, 2004., Rao and Sung, 1995)
Lentils	Reduce Breast Cancer	Flavanols	(Park et al., 2008)
	Induction of apoptosis in nasopharyngeal carcinoma cell lines	Lectin	(Chan et al., 2015)

Table 2. Protease inhibitors associated with prevention of carcinogenesis.

Protease Inhibitors	Biological Activity	References
Bowman – Brik Inhibitor	Controlled growth of sarcoma cells and induced apoptosis in postrate cancer through upregulation of connexin 43 (Cx43)	(Saito et al., 2007)
	Suppressed proliferation of breast cancer through accumulation of MAPK phosphatase-1 and induction of apoptosis and lysosome membrane permeabilization	(Joanitti et al., 2010)
	Induction of apoptosis of LNCaP prostate cancer cells, colorectal carcinogenesis and HT-29 colon cancer cells	(Kennedy et al., 2002.,Tang et al., 2009)
	Effective on the proliferation of breast and prostate cancer cells in vitro	(Magee et al., 2012; Kennedy, 1998)
	The anti-proliferative effect of TI1B, a major Bowman –Birk isoinhibitor from pea (*Pisum sativum* L.), on HT29 colon cancer cells is mediated through protease inhibition	(Clemente et al., 2012., Cruz-Huerta et al., 2015)
	Effective chemopreventive agent against prostate cancer by blocking the generation of reactive oxygen species in prostate cancer cells	(Bosland et al., 2002)
	Induced apoptosis in human breast adenocarcinoma through mitochondrial impairment and oxidative damage following proteasome 20S inhibition	(Mehdad et al., 2016)
	Suppression of proteasome function and proliferation of MCF7 breast cancer cells through accumulation of MAP kinase phosphatase-1	(Chen et al., 2005)
Kunitz-Trypsin Inhibitor	Suppressed cancer invasion and metastasis through inhibition of urokinase-type plasminogen activator (uPA) expression	(Kobayashi et al., 2004)
	Inducted apoptosis in lymphoma cells and human leukemia Jurkat cell death	(Troncoso et al., 2003; Troncoso et al., 2007)
	Hepatocyte growth factor activation inhibitors (novel Kunitz-type serine protease inhibitors : HAI-1 and HAI-2) regulate HGF-induced invasion of human breast cancer cells	(Parr and Jiang, 2006)

Table 3. Anticancer activity of different types of saponins.

Beneficial Component	Activity	References
Soyasapogenols	Suppress tumor progression by regulating macrophage differentiation into the protumoral phenotype	(Fujiwara et al., 2015)
	Antiproliferative effect of ME3738, a derivative of soyasapogenol, on hepatocellular carcinoma cell lines in vitro and in vivo	(Ogasawara, Akiba et al., 2016)
Soyasapogenol A and B	Colon anti-carcinogenic Activity	(Gurfinkel and Rao, 2003)
	Anti-proliferative properties in human breast cancer cells in vitro	(Rowlands et al., 2002)
Triterpenoidal saponins	Anti- proliferative effect on human hepatoma cells	(Wang et al., 2008)
	Apoptotic effect on breast cancer cells	(Ding, 2014)
	Anti-tumor activity by promoting apoptosis and inhibiting angiogenesis	(Bian et al., 2017)
Saponin B	Induction of macro autophagy in human colon cancer cells	(Ellington et al., 2006)
Escin (a natural mixture of triterpene saponins)	Antitumor activity against hepatocellular carcinoma	(Zhou et al., 2009)

CONCLUSION

Pulses contribute an important role not only in the healthy and balanced diet, but also reduce the risk of cancer due to the presence of several bioactive micronutrients and phytochemicals. Among the non-essential phytochemicals polyphenols, phytosterols, Saponins and dietary fibers have been reported to be potentially very effective. Such bioactives are therefore good candidates for ingredients of nutraceuticals. In developed countries, pulses are underutilized because of the greater inclination towards high energy diet comprising of animal proteins, high fat and refined carbohydrates. Given the nutrient profile and therapeutic contribution of pulses,it is warranted that an attention should be paid to encourage people to consume more pulses. The quantitative contribution of pulses to treat cancer is yet to be worked. There is a need of well-designed animal studies to evaluate the anticancer potential of unexplored and underutilized pulses. The pulses should be used as nutraceuticals where the bioactive constituents are isolated and formulated into a suitable formulation for treatment of cancer. The focus should be laid on the pulses that can act as anticancer vehicle and adjuvant to cytotoxic and targeted chemotherapy drugs and their ability to augment anticancer response.

ACKNOWLEDGEMENTS

The authors are grateful to the Head, Department of Biotechnology, Jamia Hamdard for providing the necessary facilities.Indian Council of Medical Research, New Delhi is acknowledged for providing Senior Research Fellowship to Azra Anjum (SRF/03/2018/SBSHR).

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