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Review Article

Polyphenols as Potential Dietary Cancer Prevention Strategy for Ethiopia: An Overview

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Abstract: Polyphenols, the plant secondary metabolites produced by the shikimic pathway, are categorized into flavonoids, stilbenes, lignans and phenolic acids. Fruits, vegetables, grains, spices and herbs are now known as the good source of dietary polyphenols. Polyphenols exhibit their anticancer effects by suppressing the carcinogenesis process. They modulate multiple signaling pathways, induce apoptosis and prevent DNA mutations due to their anti-oxidant property. Because of high cost and limited success of cancer therapy it has become increasingly recognized that cancer prevention is cost effective. Promotion of healthy diet, i.e., eating variety of foods which are identified as good sources of polyphenols, in regular manner and in high amount is a potential cancer prevention strategy. In this review, the up-to-date findings on cancer fighting mechanisms of dietary polyphenols are summarized. In addition, the potential of Ethiopia in using dietary polyphenols as cancer prevention strategy is elaborated.

Keywords: Polyphenol, Cancer Prevention Strategy, Carcinogenesis, Apoptosis, Antioxidant, Fruits, Vegetables, Ethiopia

1. Introduction

Polyphenols are polyhydroxylated phytochemicals produced as secondary metabolites by the shikimic pathway in plants [1, 2]. In plants, polyphenols usually act as defense agent against reactive oxygen and nitrogen species, UV light, herbivores, plant infecting fungi and bacteria, and also accelerate pollination by attractively coloring flowers [2, 3]. Structurally, polyphenols comprise one or more polyhydroxylated aromatic ring. In polyphenols that have two or more phenyl moieties, the rings are interconnected by a carbon bridge. In some of them, particularly in flavonoids, the carbon bridge connecting one ring (ring A) with the other (ring B) forms covalent bond with a hydroxyl group on the ring A and forms the third aromatic ring, ring C [4]. In most cases, polyphenols are found glycosylated with glucose or other carbohydrates. Accordingly, polyphenols are found either as glycosides and aglycones [3, 5]. Polymerization of polyphenols to lager and complex structure also occurs in plants [6].

1.1. Classification of Polyphenols

Depending on the number of aromatic rings and other structural elements, polyphenols are categorized into four groups including flavonoids, stilbenes, lignans and phenolic acids [7]. Flavonoids are the most abundant polyhenol characterized by containing two or more aromatic rings, each bearing one or more phenolic hydroxyl groups, and connected by a three carbon atoms bridge [1]. They are further classified based on the presence or absence of double bond on ring C and other structural issues. Accordingly, the subclasses of flavonoids include flavones, isoflavones, isoflavanes, flavanones, flavanols, anthocyanidins, chalcones and dihydrochalcones [5, 8].

Stilbenes contain two phenyl moieties connected by a two-carbon methylene bridge [9]. Resveratrol is a common stilbene which has been extensively studied for its anti-carcinogenic effects [8]. Moreover, phenolic acids are derivatives of benzoic acid that contains seven carbon atoms and cinnamic acid (comprising nine carbon atoms) by hydroxylation. Hydroxybenzoic acids (for example, gallotannins which are hydrolysable tannin) are found in few edible plants. The hydroxycinnamic acid includes caffeic acid, ferulic acid, *p*-coumaric acid, and sinapic acid [10]. Lignans are polyphenols having structural similarities with estrogens and classified as phytoestrogens, similar to isoflavones [11]. Lignans and their synthetic derivatives have potential applications in cancer chemotherapy and various other pharmacological effects [12].

1.2. Food Sources of Dietary Polyphenols

Many research findings indicate that consumption of plenty and variety of fruits, vegetables, legumes and grains can prevent 10 to 70% of cancer death as these foods have polyphenols [3, 6, 13]. Polyphenols are found in plants, particularly, in fruits, seeds and leaves [10]. In general, fruits, vegetables, grains, spices and herbs are the richest source of dietary polyphenols [14].

Flavonoids are present in tea, coffee, wine, onions, spinach, broccoli, berries, cherries, grapes, apples, seeds of cocoa, rosemary, corn, peaches, plums, celery, garlic, turmeric, pepper, nuts, banana, orange, lemon, mandarin, tomatoes, rice, soybean, beans, green peas, potatoes, and cabbage. While, the main food sources of phenolic acids include wheat, oat, rice, rye, barley, tef, clove buds, apples, dates, coffee beans, carrots, grapes, wine, green and black teas, mangoes and berries. Whereas, stilbenes are found in grapes, berries, plums, peanuts, and pine nuts, red wine, cabbage and spinach. Lignans are present in high concentration in linseed and in minor concentration in algae, soybean, beans, green peas, ginger, wheat, oat, rice, rye, barley, tef, vegetables, and fruits like avocado and pumpkin [4, 10, 11, 15-18].

2. Cancer Fighting Effects of Dietary Polyphenols

Cancer is a group of diseases in which genetically damaged cells proliferate autonomously and cannot respond to normal regulatory mechanisms of cell division. Consequently, those cells continue to proliferate, thereby robbing nearby normal cells nutrients and eventually crowding surrounding healthy tissue [19, 20]. Cells with damaged genetic material may form either benign or malignant tumors. Benign tumors, which grow slowly and are limited to a specific location, are not considered cancerous and rarely cause death. In contrast, malignant tumors are often fatal because they can undergo metastasis, migration through blood or lymph vessels to distant locations throughout the body. Wherever new malignant tumors arise, they interfere with normal functions of the neighboring tissue [19, 21].

Normal cell is transformed to cancerous cell through step by step process that damage the cell capacity to be abided by the normal cell proliferation and differentiation control mechanism. The cell transformation process, carcinogenesis, comprises enhanced expression of genes that promote cell survival and proliferation and/or the loss of expression of genes that control cell growth. As a result, cancerous cells develop and proliferate autonomously, irresponsive to normal regulatory mechanisms that ensure the intercellular cooperation required in multi-cellular organisms [22]. Polyphenols interfere with the carcinogenesis process by interacting with multiple signaling pathways, by inducing apoptosis, and preventing mutations due to their anti-oxidant effects.

2.1. Anti-tumerogenic Effects of Polyphenols by Modulating Cell Signaling Pathways

2.1.1. MAPK Pathway

Polyphenols, for example, epigallocatechin-3-*O*-gallate (EGCG), curcumin (CUR), resveratrol (RES), quercetin and apigenin have demonstrated potent anti-cancer activity by suppressing cancerous cell proliferation and inducing cell cycle arrest in diversified mechanisms. The main way is by affecting the MAPK pathway in variety of cancers by suppressing epidermal growth factor receptor (EGFR) phosphorylation and/or inhibiting *fos* expression and/or inhibiting ERK1/2 activation [11, 23, 24].

2.1.2. NF-κB-Mediated Pathway

Polyphenols like EGCG, delphinidin, anthocyanins, caffeic acid, CUR and RES exhibit their anti-cancer effects as they inhibit the constant activation of the NF-κB-mediated pathway which is a common feature of tumor cells. Up-regulated activation of the NF-κB-mediated pathway results in high production of inflammatory mediators such as tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, prostaglandin E2 (PGE2), reactive oxygen species (ROS), and development of chemoresistance in tumor cells. These lead to inhibition of apoptosis and increased metastatic capability [3, 11, 24-30].

2.1.3. Hedgehog (Hh) Signaling Pathway

Dietary polyphenols have demonstrated cancer fighting effect by down regulating the Hedgehog (Hh) signaling pathway. Hh pathway is responsible for induction of cell differentiation, morphogenesis and organogenesis in vertebrates' embryogenetic processes. Hh pathway is also has curtail regulatory activity in cell proliferation and survival. Particularly, activation of Hh pathway is the mechanism by which stem cells, for example, hematopoietic stem cell, promote regeneration and expansion. However, sustained activation of Hh pathway leads to increased expression of glioma-associated oncogene I (GLI) transcription factor which enhances gene expression and synthesis of proteins promoting carcinogenesis in up-regulating cell survival and proliferation. Accordingly, a cell with sustained activation of Hh pathway develops migration and invasion capacity [32–34].

Hh signaling pathway is initiated by the binding of the Hh protein ligand to its cell surface receptor known as PTCH1. This, in turn, activates the genetic factor GLI which induces gene expression and protein synthesis. Hh ligand has different isoforms in different tissues. The common Hh isoforms include sonic Hedgehog (SHh), desert Hedgehog (DHh) and Indian Hedgehog (IHh). Polyphenols including CUR, EGCG, genistein, apigein, quercetin and RES have shown anti-cancer effect by modulating the Hh downstream signaling pathway by inhibiting expression of Hh ligand, GLI and PTCH1 proteins [11, 34-38].

2.2. Cancer Fighting Effects of Polyphenols by Modulating Apoptosis

Polyphenols have demonstrated also pro-apoptotic effect by up-regulation of p53 expression, increasing Bax/Bcl-2 ratio, blocking Akt activity and suppressing the expression of survivine which results in cancer cell death [40–43]. During chronic inflammation, in which NF-κB-mediated pathway is up-regulated, expression of anti-apoptotic genes such as the caspase-8 inhibitor and members of the Bcl2 family of apoptosis regulators is enhanced. Therefore, polyphenols inhibit this pathway and enhance programmed death of cancer cells [28, 43-45].

2.3. Anti-tumerogenic Effects of Polyphenols by DNA Mutation Prevention (Antioxidant Activity)

Dietary polyphenols exhibit cancer chemo-prevention potential due to their anti-oxidant property [13]. Exposure to pathogenic bacteria or virus leads to the production of reactive oxygen and nitrogen species (ROS and RNOS) from immune cells as a means of killing the pathogens. However, persistent and long term immune responses can cause homeostatic imbalance of the immune regulatory functions, leading to irreversible damage of the tissues. Besides, over exposure to various stimuli such as pollutants, smoke, drugs, xenobiotics, ionizing radiation and heavy metal ions, induces excess production of ROS and RNOS including nitric oxide, hydroxyl radical and superoxide anion, peroxyl radicals, hypochlorous acid (HOCl) and peroxynitrous acid (ONOOH). Over production of these radicals results in oxidative stress which possibly causes DNA mutation. Accordingly, polyphenols like quercetin inhibit DNA mutation by interrupting the propagation stage of the lipid autoxidation chain reactions as effective radical scavengers or act as metal chelators to convert hydroperoxides or metal prooxidants into stable compounds [12, 13, 14, 23, 24, 46].

Additionally, dietary polyphenols exhibit their anti-oxidant activity, indirectly, by enhancing the expression of antioxidant enzymes such as superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione peroxidase (GPO), heme oxygenase-1 (HO-1) and catalase (CAT) mainly by activating Nrf2 pathway [48–50].

3. Dietary Polyphenols as Cancer Prevention Strategy for Ethiopia

Cancer is becoming a leading cause of death globally. It is estimated that cancer kills over 7.9 million people globally every year constituting close to 13% of total deaths worldwide. In Ethiopia, cancer accounts for about 5.8% of total national mortality. It is estimated that the annual incidence of cancer in Ethiopia is around 60,960 cases and the annual mortality is over 44,000 [51]. The occurrence of cancer is increasing because of the growth and aging of the population, as well as an increasing prevalence of established risk factors, such as smoking, overweight, physical inactivity, and changing reproductive patterns associated with urbanization and economic development [52, 53]. Lung and breast cancer are the most frequently diagnosed cancers and the leading causes of cancer death in men and women, respectively, both overall and in less-developed countries [54]. The most prevalent cancers in Ethiopia among the adult population are breast cancer (30.2%), cancer of the cervix (13.4%) and colorectal cancer (5.7%). About two-thirds of reported annual cancer deaths occur among women [51].

The burden of cancer on society, particularly, in developing countries like Ethiopia is escalating. However, Ethiopia lacks cancer control strategy until 2015. The first cancer control plan was developed in 2015 in the history of the countries health system. This plan included promotion of healthy diet and physical activity as a cancer prevention strategy. Accordingly, this review article is aimed in giving insight on using fruits, vegetables, spices, grains and herbs as sources of dietary polyphenols which have proven anti-cancer effect. Therefore, the author of this review article strongly believes that the article will eminently contribute to the attempt of implementing the cancer control plan of Ethiopia.

Because of high cost and limited success of cancer therapy, it has become increasingly recognized that cancer prevention is cost effective. Promotion of healthy diet as the cancer prevention strategy is with a double benefit. Because fruits, vegetables, spices, grains and herbs are not only the food sources of polyhenols but also the good sources of minerals including vitamin which are essential for human health. Besides, Ethiopia is the home of large number of species of fruits, vegetables, spices, grains and herbs which are identified as good sources of polyphenols. In addition, Ethiopia has a high potential of production of tropical, sub-tropical and temperate fruits, vegetables, spices, grains and herbs as she has favorable climate and edaphic conditions [55]. Therefore, dietary cancer prevention strategy is cost effective, easy and recommendable for Ethiopia.

Moreover, poor bioavailability of dietary polyphenols in human body hinders *in vivo* anticancer effects, especially when taken singly [11]. Whereas, using combination of polyphenols can exert significantly enhanced anticancer effect at considerably lower concentration. Synergetic action of phenolic mixtures additionally results in concurrent impact on different carcinogenic pathways consequentially contributing to significant cancer control and prevention effects of dietary polyphenols [3]. High intake of foods containing polyphenols has been linked to lowered risk of common chronic diseases including cancer [14]. Therefore, regular intake of foods containing polyphenols in high amount and in higher possible variety is recommended diet for cancer prevention.

4. Conclusions and Future Directions

Eating variety of foods which are identified as good sources of polyphenols, particularly, fruits, vegetables, spices, grains and herbs, in regular manner, and in high amount is a potential cancer prevention strategy. Since, Ethiopia is the home for these foods and the country has a high potential of production of tropical, sub-tropical and temperate fruits, vegetables, spices, grains and herbs, Ethiopia has a high potential of dietary cancer prevention capacity by promoting healthy diet.

However, a detailed guideline on how to prepare and use foods that are identified as good sources of dietary polyphenols is highly required for Ethiopia. Furthermore, awareness creation, for the general public, on the anticancer effects of dietary polyphenols and how to prepare and use the foods identified as sources of polyphenols is highly recommended.

Abbreviations

UV	Ultra violet.
EGFR	Epidermal growth factor receptor.
DNA	Deoxyribonucleic acid.
PTCH1	Protein patched homolog 1 Homo sapiens.
MAPK	Mitogen activated protein kinase.
EGCG	Epigallocatechin-3-*O*-gallate.
CUR	Curcumin.
RES	Resveratrol.
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2.
NF-κB	Nuclear factor kappa B.
Nrf2	Nuclear factor erythroid 2-related factor.
TNF	Tumor necrosis factor.
IL-1	Interleukin-1.
PGE2	Prostaglandin E2.
ROS	Reactive oxygen species.
RNOS	Reactive nitrogen species.
Hh	Hedgehog.
GLI	Glioma-associated oncogene I.
SHh	Sonic Hedgehog.
DHh	Desert Hedgehog.
IHh	Indian Hedgehog.
Bax	B-cell lymphoma 2 associated X protein.
Bcl-2	B-cell lymphoma 2.
Akt	Protein kinase B.
ONOOH	Peroxynitrous acid.

References

[1] Tressera-Rimbau, Arranz S, Eder M, Vallverdú-Queralt A. Dietary Polyphenols in the Prevention of Stroke: Review Article. Oxidative Medicine and Cellular Longevity; 2017; https://doi.org/10.1155/2017/7467962.

[2] Lin D, Xiao M, Zhao J, Li Z, Xing B, Li X, Kong M, Li L, Zhang Q, Liu Y, Chen H, Qin W, Wu H, Chen S. An Overview of Plant Phenolic Compounds and Their Importance in Human Nutrition and Management of Type 2 Diabetes: Review. Molecules 2016; 21: 1374.

[3] Mojzer B, Hrnˇciˇc M, Škerget M, Knez Ž, Bren U. Polyphenols: Extraction Methods, Antioxidative Action, Bioavailability and Anticarcinogenic Effects: Review. Molecules 2016; 21: 901.

[4] Mocanu M, Nagy P, Szöllosi J. Chemoprevention of Breast Cancer by Dietary Polyphenols: Review. Molecules 2015; 20: 22578–22620.

[5] Tsao R. Chemistry and Biochemistry of Dietary Polyphenols: Review. *Nutrients* 2010; *2*: 1231-1246.

[6] Cardonaa F, Andrés-Lacuevac C, Tulipania S, Tinahones F, Queipo-Ortuño M. Benefits of polyphenols on gut microbiota and implications in human health: Review. Journal of Nutritional Biochemistry 2013; 24: 1415–1422.

[7] Ganesan K, Xu B. A Critical Review on Polyphenols and Health Benefits of Black Soybeans. Nutrients 2017; 9: 455.

[8] Niedzwiecki A, Roomi M, Kalinovsky T, Rath M. Anticancer Efficacy of Polyphenols and Their Combinations: Review. Nutrients 2016; 8: 552.

[9] Lall R, Syed D, Adhami V, Khan M, Mukhtar H. Dietary Polyphenols in Prevention and Treatment of Prostate Cancer: Review. *Int. J. Mol. Sci.* 2015; *16*: 3350-3376.

[10] Ding Y, Yao H, Yao Y, Fai L, Zhang Z. Protection of Dietary Polyphenols against Oral Cancer: Review. *Nutrients* 2013; *5*: 2173-2191.

[11] Fantini M, Benvenuto M, Masuelli L, Frajese G, Tresoldi I, Modesti A, Bei R. *In Vitro* and *in Vivo* Antitumoral Effects of Combinations of Polyphenols, or Polyphenols and Anticancer Drugs: Perspectives on Cancer Treatment: Review. *Int. J. Mol. Sci.* 2015; *16*: 9236-9282.

[12] Moga M, Dimienescu O, Arvatescu C, Mironescu A, Dracea L, Ples L. The Role of Natural Polyphenols in the Prevention and Treatment of Cervical Cancer—An Overview: Review. Molecules 2016; 21: 1055; doi:10.3390/molecules21081055.

[13] Mileo A, Miccadei S. Polyphenols as Modulator of Oxidative Stress in Cancer Disease: New Therapeutic Strategies: Review article. Oxidative Medicine and Cellular Longevity. 2016; http://dx.doi.org/10.1155/2016/6475624.

[14] Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Current Opinion in Food Science 2016; 8:33–42.

[15] Fatemeh S, Saifullah R, Abbas F, Azhar M. Total phenolics, flavonoids and antioxidant activity of banana pulp and peel flours: influence of variety and stage of ripeness. International Food Research Journal 2012; 19(3): 1041-1046.

[16] Zdunić G, Menković N, Jadranin M, Novaković M, Šavikin K, Živković J. Phenolic compounds and carotenoids in pumpkin fruit and related traditional products. *Hem. Ind. 2016;* 70 (4): 429–433.

[17] Boka B, Woldegiorgis A, Haki G. Antioxidant Properties of Ethiopian Traditional Bread (*Injera*) as Affected by Processing Techniques and Tef Grain (Eragrostistef (Zucc.)) Varieties. Canadian Chemical Transactions 2013; 1(1): 7-24.

[18] Tanvir E, Hossen M, Hossain M, Afroz R, Gan S, Khalil M, Karim N. Antioxidant Properties of Popular Turmeric *(Curcuma longa)* Varieties from Bangladesh. Journal of Food Quality; 2017; https://doi.org/10.1155/2017/8471785.

[19] Hejmadi M. Introduction to Cancer Biology. Denmark: BoonBooks.com; 2010.

[20] Strayer S, Rubin E. Neoplasia. In: Rubin R, Strayer S, Rubin E, editors. Pathology: Clinicopathologic Foundations of Medicine. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2012. P. 158-212.

[21] American Cancer Society. Cancer facts and figures 2017. Atlanta: American Cancer Society; 2017.

[22] Malarkey E, Hoenerhoff M, Maronpot R. Carcinogenesis: Mechanisms and Manifestations. In: Haschek W, Rousseaux C, Walling M, editors. Haschek and Rousseaux's Handbook of Toxicologic Pathology. 3rd ed. USA: Academic press; 2013. P. 107–146.

[23] Mebratu Y, Tesfaigzi Y. How ERK1/2 Activation Controls Cell Proliferation and Cell Death Is Subcellular Localization the Answer?*Cell Cycle*2009; 8(8): 1168–1175.

[24] Khoogar R, Kim B, Morris J, Wargovich M. Chemoprevention in gastrointestinal physiology and disease. Targeting the progression of cancer with natural products: a focus on gastrointestinal cancer. Am J PhysiolGastrointest Liver Physiol2016; 310: G629–G644.

[25] Busch F, Mobasheri A, Shayan P, Lueders C, Stahlmann R, Shakibaei M. Resveratrol Modulates Interleukin-1 β-induced Phosphatidylinositol 3-Kinase and Nuclear Factor *k*B Signaling Pathways in Human Tenocytes. The Journal of Biological Chemistry 2012; 287 (45): 38050–38063.

[26] Chen W, Li Z, Bai L, Lin Y. NF-kappaB, a mediator for lung carcinogenesis and a target for lung cancer prevention and therapy. Front Biosci. 2012; 16: 1172–1185.

[27] Batra P, Sharma A. Anti-cancer potential of flavonoids: recent trends and future perspectives. Biotech 2013; 3:439–459.

[28] Min K, Known T. Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate: Review Article. Integr Med Res; 2 0 1 4: 16–24.

[29] Xia Y, Shen S, Verma I. NF-κB, an active player in human cancers. *Cancer Immunol Res*. 2014; 2(9): 823–830. doi:10.1158/2326-6066.CIR-14-0112.

[30] Lin B, Gong C, Song H, Cui Y. Effects of anthocyanins on the prevention and treatment of cancer: Review article. British Journal of Pharmacology 2017; 174: 1226–1243.

[31] Cas M, Ghidoni R. Cancer Prevention and Therapy with Polyphenols: Sphingolipid-Mediated Mechanisms: Review. Nutrients 2018; 10: 940; doi:10.3390/nu10070940.

[32] Gupta S, Takebe N, LoRusso P. Targeting the Hedgehog pathway in cancer: Review. TherAdv Med Oncol. 2010; 2(4): 237 – 250.

[33] Armas-López L, Zúñiga J, Arrieta O, Ávila-Moreno F. The Hedgehog-GLI pathway in embryonic development and cancer: implications for pulmonary oncology therapy: Review. Oncotarget, 2017; 8(36): 60684-60703.

[34] Skoda A, Simovic D, Karin V, Kardum V, Vranic S, Serman L. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. *Bosn J Basic Med Sci.* 2018; 18(1):8-20.

[35] Ślusarz A, Shenouda N, Sakla M, Drenkhahn S, Narula A, MacDonald R, Besch-Williford C, Lubahn D. Common Botanical Compounds Inhibit the Hedgehog Signaling Pathway in Prostate Cancer. Cancer Res 2010; 70(8): 3382–3390.

[36] Szkandera J, Kiesslich T, Haybaeck J, Gerger A, Pichler M. Hedgehog Signaling Pathway in Ovarian Cancer: Review. *Int. J. Mol. Sci.* 2013; *14*: 1179-1196.

[37] Gao Q, Yuan Y, Gan H, Peng Q. Resveratrol inhibits the hedgehog signaling pathway and epithelial-mesenchymal transition and suppresses gastric cancer invasion and metastasis. Oncology Letters 2015; 9: 2381-2387.

[38] Amawi H, Ashby C, Samuel T, Peraman R, Tiwari A. Polyphenolic Nutrients in Cancer Chemoprevention and Metastasis: Role of the Epithelial-to-Mesenchymal (EMT) Pathway: Review. Nutrients 2017; 9: 911; doi:10.3390/nu9080911.

[39] Yao Z, Han L, Chen Y, He F, Sun B, Kamar S, Zhang Y, Yang Y, Wang C, Yang Z. Hedgehog signalling in the tumourigenesis and metastasis of osteosarcoma, and its potential value in the clinical therapy of osteosarcoma: Review article. Cell Death and Disease 2018; 9:701.

[40] Cimino S, Sortino G, Favilla V, Castelli T, Madonia M, Sansalone S, Russo G, Morgia G. Polyphenols: Key Issues Involved in Chemoprevention of Prostate Cancer: Review Article. Oxidative Medicine and Cellular Longevity 2012; doi:10.1155/2012/632959.

[41] Rodríguez M, Estrela J, Ortega Á. Natural Polyphenols and Apoptosis Induction in Cancer Therapy: Review Article. CarcinogeneMutagene2013; S6; http://dx.doi.org/10.4172/2157-2518.S6-004.

[42] Chen X, Li Y, Lin Q, Wang Y, Sun H, Wang J, Cui G, Cai L, Dong X. Tea polyphenols induced apoptosis of breast cancer cells by suppressing the expression of Survivin. Scientific Reports 2014; 4: 4416, doi: 10.1038/srep04416.

[43] Oz H, Ebersole J. Green Tea Polyphenols Mediated Apoptosis in Intestinal Epithelial Cells by A Fadd-Dependent Pathway. J Cancer Ther. 2010; 1(3): 105–113.

[44] Bhat M, Farhat S, Singh Z, Shoib S. Plant Derived Polyphenols, Other Drugs Targeting NF-κB and its Therapeutic Implications. BBB 2014; 2(2): 422-429.

[45] Zhang XA, Zhang S, Yin Q, Zhang J. Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B pathway. Phcog mag 2015; 11: 404 – 409.

[46] Kim HS, Quon MJ, Kim J. New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate: Mini Review. Redox Biology 2014; 2: 187–195.

[47] Hu ML. Dietary Polyphenols as Antioxidants and Anticancer Agents: More Questions than Answers: Review article. Chang Gung Med J 2011; 34(5): 449 – 460.

[48] Taha R, Blaise G. Nrf2 activation as a future target of therapy for chronic diseases: Review. *Functional Foods in Health and Disease* 2014; 4(11):510-523.

[49] Smith RE, Tran K, Smith CC, McDonald M, Shejwalkar P, Hara K. The Role of the Nrf2/ARE Antioxidant System in Preventing Cardiovascular Diseases: Review. Diseases 2016; 4: 34; doi:10.3390/diseases4040034.

[50] Martínez-Huélamo M, Rodríguez-Morató J, Boronat A, Torre R. Modulation of Nrf2 by Olive Oil and Wine Polyphenols and Neuroprotection. Antioxidants 2017; 6: 73; doi:10.3390/antiox6040073.

[51] Federal Ministry of Health Ethiopia: National Cancer Control Plan 2015/2016-2020. Addis Ababa, Ethiopia, Federal Ministry of Health, 2015.

[52] Kamil N, Kamil S. Global Cancer Incidences, Causes and Future Predictions for Subcontinent Region. Systematic Reviews in Pharmacy 2015; 6(1):13-17.

[53] Torre L, Bray F, Siegel R, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. CA CANCER J CLIN 2015;65:87–108.

[54] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. Available from: http://globocan.iarc.fr, accessed on 23/10/2018.

[55] Hunde NF. Opportunity, Problems and Production Status of Vegetables in Ethiopia: A Review. J Plant Sci Res. 2017; 4(2): 172.